HealthTech IV

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Semiannual Report
April 2004 – September 2004

Submitted to:
United States Agency for International Development (USAID)

Submitted by:
Program for Appropriate Technology in Health (PATH)
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Highlights and Milestones of the Past Six Months

- In September 2004, BD, PATH, and Pfizer agreed to preliminary structure of supply agreement for license to use the Uniject™[1] device for delivery of Pfizer's new DMPA product.
- Final data analysis of the delivery kit study in Tanzania demonstrated lower rates of sepsis and cord infection among kit users and their infants. The information can be useful to donors in decisions about delivery kit projects and to managers in decisions about the use of delivery kits in their programs.
- Prevention of freezing of vaccines was the primary topic of discussion among UN policymakers and PATH at the recently organized Technology Operations Panel meetings at WHO. The discussions were based primarily on data generated in HealthTech studies. The topic was also a high priority issue at the recent Tech Net meetings.
- Results of the India study of needle removers, where 125,000 needles were removed after use, have been completed and showed that needle removal is acceptable and desired. Subsequently 14,000 needle removers are being purchased by the government of India for use in Andhra Pradesh.
- The Uniject DP device and Exacta-Med dispenser have been identified as feasible options for delivery systems for single-dose packaging of nevirapine oral suspension. Stability and acceptability studies of both are ongoing. Initial stability study results suggest nevirapine in Uniject DP is stable for four months at varying temperatures. Exacta-Med is stable for two months and PATH is working to optimize packaging in order to extend stability.
- "Improving Topical Microbicide Applicators for Use in Resource-Poor Settings" authored by HealthTech staff was published in the July 2004 issue of the *American Journal of Public Health*. (Attachment 1)
- The technical know-how for production of the rapid gonorrhea test have been transferred to Orchid Biomedical, a commercial manufacturer in India.
- Initial analysis of results of the rapid chlamydia test using clinical cervical swab samples was completed and demonstrated 60% sensitivity and 98% specificity as compared to strand displacement amplification.
- The results of the study of serodiagnosis of tuberculosis using rapid tests in Botswana, which utilized the HealthTech TB immunochromatographic test were published in the July 2004 issue of *Clinical Infectious Diseases*. (Attachment 2)
- An articled entitled "Delivering Microbicides: Considering Key Factors in Applicator Design" by HealthTech staff was published in the *Microbicide Quarterly*. (Attachment 3)

[1] Uniject is a trademark of BD.

Milestones and Accomplishments for Past HealthTech Technologies

- The recommendations of a select group of international maternal health specialists, who met in 2003 to develop a list of proven and promising technologies to reduce maternal mortality, included oxytocin in the Uniject device as the highest priority technology. The results of the meeting were published in *Lancet* 2004 in an article entitled "New and Underused Technologies to Reduce Maternal Mortality." (Attachment 4)

- Another article by HealthTech project director Michael Free, resulting from that meeting, was published in 2004 in the *International Journal of Gynecology and Obstetrics*. The article, entitled "Achieving Appropriate Design and Widespread Use of Health Care Technologies in the Developing World" reflects experience gained through the 17-year history of the HealthTech program. (Attachment 5)

- For the first time in India, three health care majors, Panacea Biotec, Chiron Vaccines and BD are working together for a unique "Simple & Safe" concept in immunization—combination vaccines in a single-use delivery system, the BD Uniject device. The combination vaccine would simplify the immunization process and minimize the need for repeated injection shots, whereas the BD Uniject single-use prefill device will make it safer and more accessible for the recipient.

- P.T. Biofarma/Indonesia has received formal WHO approval of hepatitis B vaccine filled in the Uniject device for purchase by UN agencies. They had already received approval of the device from the Indonesian FDA. Hepatitis B vaccine in Uniject is now used routinely for birth dose throughout Indonesia.

- The *Anemia Detection Manual for Program Managers*, written and published several years ago by HealthTech, is being translated for use in Tibet and Nepal, where it is used in workshops and considered to be of great value for field workers.

- Lee Laboratories, the licensee for the syphilis immunochromatographic test developed under HealthTech, reports that during a trial of rapid syphilis tests by the Centers for Disease Control and Prevention, the HealthTech test had excellent results: overall sensitivity 100% and specificity 96%.

Immunization and Injection Technologies

Cold Chain Technologies

Health Need Addressed

Improperly maintained or outdated refrigeration equipment, poor compliance with cold chain procedures, inadequate monitoring, and poor understanding of the dangers of vaccine freezing contribute to the weakness of the current vaccine cold chain. Emphasis has long been placed on keeping vaccines cold, with less attention devoted to prevention of vaccine damage from freezing. Published reports and field evidence generated under HealthTech support anecdotal reports and demonstrate that accidental freezing of vaccines in the cold chain is commonplace, potentially resulting in widespread delivery of vaccines whose potency has been compromised.

HealthTech IV Solution and Potential Impact

Cold chain technologies, such as the vaccine vial monitor (VVMs), new refrigeration technologies, and new vaccine presentations strengthen immunization programs' ability to provide outreach services, improve the reliability of vaccine storage and transport, and reduce unnecessary wastage of valuable vaccines. Most importantly, these technologies will reduce the delivery of ineffective vaccines. Supported by the USAID-funded HealthTech program, and in collaboration with other organizations, PATH is addressing these priorities. Efforts include fostering changes in cold chain policies and an improved global awareness of the magnitude of accidental vaccine freezing. Evaluation and development is directed toward new technologies that improve vaccine storage and transport, prevent accidental freezing, and increase cold chain capacity for important new vaccines and presentations.

Example of freeze-prevention materials

Ultimate Goals and Objectives of HealthTech Project

- Increase awareness of the consequences of freezing certain vaccines and expand immunization outreach.
- Model options for a flexible vaccine cold chain that can increase capacity for future vaccines and single-dose presentations.
- Improve cold chain reliability, performance, and affordability with new vaccine refrigeration and carrier technologies.

Status of Project as of September 2004

- Participating in the newly formed WHO Product Quality System (PQS) group to develop specifications on freeze prevention for new refrigerators.
- Participating in the WHO working group to review cold chain freezing issues and develop a global action plan and guidelines.

- Currently field testing the SolarChill refrigerator in Senegal and Indonesia.
- Identifying and laboratory testing of promising new refrigerator technologies.
- Identified new component technologies that could overcome most cold chain problems. PATH is negotiating with the holders of these technologies to bring these components together into an integrated freeze-proof refrigerator with hybrid energy capability that can operate independent of electricity supply when necessary.

Milestones expected in the past six months	Achievements and progress towards milestones
Conduct field evaluations of the SolarChill vaccine refrigerator in Indonesia and Senegal in 2004.	Began March 2004.
Collect further evidence of a two-temperature cold chain approach to prevent vaccine freezing and reduce distribution costs in Indonesia.	Ongoing in Indonesia.
Continue to collaborate with WHO, UNICEF, and vaccine manufacturers through Technology Operations Panel (TOP).	At the TOP meeting in March, WHO called for a working group to review cold chain policy regarding freezing and out-of-cold-chain options.
Explore with WHO ways to accelerate the introduction of VVMs on all vaccines to facilitate the ability of countries to remove heat-stable vaccines from the cold chain.	WHO-UNICEF working group will review feasibility of VVM-managed, out-of-cold-chain vaccination.
Assist countries in assessing freezing in the cold chain using the PATH-developed protocol.	Freeze study in Mozambique completed—100% freezing found. WHO is in the process of making the PATH study protocol into a WHO document.
Identification of improved refrigeration technologies.	Conducted lab evaluation of "Twinbird" and "Action Africa" refrigerators that showed potential for vaccine storage. Currently discussing design refinements with manufacturers. SolarChill evaluation in Indonesia and Senegal ongoing—currently making field modifications to improve performance. VaxiCool®[1] has shifted its priorities away from public health.
Model flexible policies for management of the cold chain in several countries. Work with WHO on a policy document on the "flexible cold chain" to assist countries with implementation.	Participating in WHO cold chain working group recommendations and strategy development.

[1] VaxiCool is a registered trademark of Energy Storage Technologies, Inc., Dayton, OH.

Problems encountered	Actions taken or plans to resolve
Inability to convince VaxiCool manufacturer to redesign VaxiCool for solar applications.	VaxiCool is still considered a viable option. Company under new ownership. Have recently restarted talks with new owners.
WHO reluctance to act decisively on vaccine freezing as a high priority issue.	Continued discussions with WHO and UNICEF representatives. Continued collection of field evidence to demonstrate severity of problem. Further discussions of evidence required to prioritize freezing.
Reluctance of countries to release data on cold chain temperatures that verifies a high level of accidental vaccine freezing.	Work with partners and WHO to encourage countries to conduct and disseminate information documenting cold chain performance, including vaccine freezing.
Field evaluation of the SolarChill design revealed excessive temperature swings.	Work with manufacturers to identify modifications; continue field evaluation of refined units.

Milestones expected in the next six months	Planned activities to reach those milestones
New WHO policies and guidelines to prevent vaccine freezing.	Incorporation of PATH's freeze study protocol into WHO document. Develop revised cold chain recommendations and policy with WHO. Complete PQS process to develop specifications for freeze-proof refrigerators. Continue meetings with WHO and UNICEF to review country data.
Raise awareness of vaccine freezing problem.	Publish literature review of occurrence of vaccine freezing and epidemiological impact of freezing.
Develop freeze-prevention plan as part of national EPI guidelines in Indonesia.	Analyze study data and discuss with ministry of health (MOH) how to develop national freeze-prevention policy and procedures.
Refine improved refrigerator technologies.	Refine SolarChill design to improve performance and ensure freeze protection. Evaluate improved Twinbird vaccine refrigerator; continue design refinement with manufacturer. Promote design refinement decisions with VaxiCool manufacturer.

Safe Medical Waste

Health Need Addressed

Each year, more than 16 billion injections are administered worldwide. In some regions, 17% to 75% are estimated to be with reused, unsterilized injection equipment.[2] Unsafe reuse has been estimated to cause 20 million hepatitis B infections, 2 million hepatitis C infections, and 250,000 HIV infections annually.[3] The main tool to prevent reuse of unsterile syringes and needles is use of auto-disable and safety needles and syringes. However, most syringes currently in use do not prevent reuse. Appropriate sharps and syringe waste management play a critical role in safe injection by disabling syringes to prevent reuse, facilitating the safe and immediate disposal of contaminated sharps, reducing infectious waste volume, and facilitating ultimate disposal. It is important that waste is not dangerous for health service providers or the community, and that people are protected from hazards when collecting, handling, storing, transporting, treating, or disposing of sharps waste.

Safe injection is impaired by the lack of policies on proper disposal of sharps, appropriate equipment, and evidence of cost-effective systems. Currently, sharps waste is dangerous to the community and health care workers; and waste handlers are not protected from hazardous sharps when collecting, storing, transporting or disposing of sharps waste.[4,5,6]

HealthTech IV Solution and Potential Impact

The use of needle removers to separate the needle from the syringe immediately after use reduces the risk of potential infection to patients, health care workers, waste handlers, and the community by:

- Immediately isolating the contaminated sharp.
- Preventing syringe and needle reuse (since the needle remover also destroys the syringe).
- Reducing needle-stick injury risk for waste handlers and scavengers.

By separating the sharp from the syringe, waste disposal systems are more effective and efficient. They:

- Provide an immediate option for sharps disposal via protected needle pits.
- Heighten awareness of contaminated sharps by creating behavioral practices specific to contaminated needle waste management.

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[2] Hutin Y, Hauri A, Armstrong G. Use of injections in healthcare settings worldwide, 2000: literature review and regional estimates. *British Medical Journal*. 8 November 2003;327(7423):1075.

[3] Hutin Y, Hauri A, Chiarello L, et al. Best infection control practices for intradermal, subcutaneous, and intramuscular needle injections. *Bulletin of the World Health Organization*. 2003;81(7):491-50.

[4] Jie L. Rapid Assessment of Injection Practices in China, Final Report to the Ministry of Health of China and the Secretariat of SIGN, December 2002.

[5] Dicko M, Oni AQ, Ganivet S, et al. Safety of immunization injections in Africa: not simply a problem of logistics. *Bulletin of the World Health Organization*. 2000;78(2):163-169.

[6] Rajasekara M, Sivagnanam G, Thirumalailolundusubramainan P, et al. Injection practices in southern part of India. *Public Health.* 2003;117:208-231.

- Reduce disposal costs by decreasing or eliminating the requirements for transport and safety boxes.

Taking into account developing-country injections, reuse, needle-stick injury and infections caused by reuse, we have estimated that needle removal devices could, by 2013:

- Avert more than 9 million hepatitis B, hepatitis C, and HIV infections over a ten-year period (based on an assumption of 20% adoption of needle remover devices by 2013 globally).
- Reduce the overall systems cost of injections (including treatment for inadvertent infection caused by unsafe injection) by more than US$70 million.
- Reduce the cost per safe injection from US$0.077 to US$0.065 over ten years.

Ultimate Goals and Objectives of HealthTech Project

The project goal is to advance, test, and introduce safe needle removal and disposal systems for health centers and outreach services. The objectives are provided below in the status update.

Status of Project as of September 2004

A new evaluation is being planned for the BD Hub-Cutter device in family-planning settings, and new disposal methods are being evaluated.

Milestones expected in the past six months	Achievements and progress towards milestones
Determine state of point-of-care needle removal systems (NRS).	Evaluated battery-operated needle remover—determined it to be unsuitable for developing-country settings.
Optimize NRS for use in developing-world health centers and outreach services.	Developed early prototype of Hopkins NRS.
Validate NRS in developing-world settings.	Bench-tested BD Hub Cutter. Finalized protocol and identified sites in Uganda for evaluation in family-planning settings.
Align global and national policies to accommodate NRS use.	Data from evaluation of NR devices in India submitted for publication in peer-review journal.
Introduce NRS into practice.	Developed training materials for Balcan device for use in PEPFAR country programs.
Evaluate and refine needle removal and syringe disposal systems.	Completed bench testing of sharps barrel and funnel.

Problems encountered	Actions taken or plans to resolve
For the BD Hub Cutter evaluation, it is difficult to track IX syringes once they reach Uganda. The numbers of IX's shipped are still fairly small and once in Uganda, they are distributed by Population Services International (PSI) through the private sector, not the MOH or NGO clinics.	Rather than focusing on the contribution of the BD Hub Cutter towards reduction of waste volume, we will focus on the acceptability of the device, its design, and its fit within family-planning systems. We plan to evaluate the device's use in government, NGO, and private family-planning settings that deliver Depo Provera, regardless of the type of syringe used.

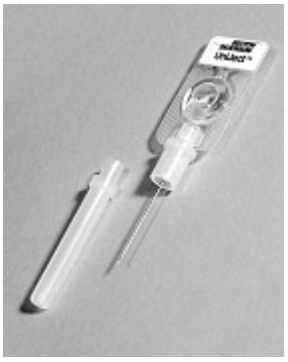
Milestones expected in the next six months	Planned activities to reach those milestones
Design of Hopkins NR prototype finalized.	Complete design on interface between plug and scissors. Build prototype for bench testing. Make final refinements for design specifications for field test prototype molds.
Acceptability, fit, and function of BD Hub Cutter evaluated in family-planning settings.	Receive protocol approval for BD Hub Cutter study. Conduct training in Uganda. Collect and analyze data.
Appropriate sites for field-testing of the Hopkins NR identified.	Screen potential sites for Hopkins NRS evaluation; identify funding for study.
Generic procurement specifications for NR disseminated.	Finalize specifications and distribute.
User materials for NR use developed/disseminated.	Produce set of NRS user and training materials
Design package for HealthTech-designed outreach device in public domain.	Send design information for HealthTech device to SIGN and WHO web sites. Provide assistance as appropriate to interested manufacturers.
Acceptability of Balcan device evaluated after one year of use in a developing-country immunization setting.	Undertake evaluation of Balcan NR in Senegal and PEPFAR introduction sites.
Acceptability of sharps barrel as an alternative to the protected needle pit evaluated in a developing-country setting.	Obtain protocol approval and undertake evaluation in Senegal.
Bench testing of electric syringe melter completed.	Receive melter and conduct testing.

Gentamicin in Uniject™ Devices

Health Need Addressed

WHO estimates that at least four million neonatal deaths (i.e., death during the first 28 days of life) occur around the world every year. Severe bacterial infections are major contributors of newborn morbidity and mortality. In the developing-world each year, an estimated 30 million children develop an infection during the neonatal period, and infectious diseases account for over one-third of all neonatal deaths. In 2000, a WHO advisory committee recommended intramuscular injections of ampicillin and gentamicin as the standard therapy for these bacterial infections and the treatment of neonatal septicemia, meningitis, and pneumonia. Case-fatality rates for severe bacterial infections are high in part due to not administering or delaying the administration of necessary antibiotics. Therefore, it is important that newborns with these infections receive immediate treatment, even before the infectious agent is known. When neonatal infections occur, many deaths can be avoided if the signs are recognized early and the disease is treated promptly.

HealthTech IV Solution and Potential Impact



Uniject single-dose prefill injection device

To improve neonatal survival from infectious diseases, Uniject™[1] injection devices prefilled with a single dose of gentamicin (hereafter called "gentamicin-Uniject") could be easily transported and used in a home setting with an oral antibiotic when the signs of a neonatal infection are first detected. Community-based health workers could be trained to use the gentamicin-Uniject device and a complementary oral antibiotic in order to extend the accessibility and facilitate the administration of antibiotics for early treatment of neonatal infections. Furthermore, gentamicin-Uniject devices could potentially be incorporated into the revised integrated management of childhood illness guidelines, which have been adapted for acute management of common infectious neonatal illnesses. If gentamicin-Uniject is used safely, properly, and efficiently for infants with severe bacterial infections, Uniject devices could make a significant contribution to reducing neonatal mortality in developing countries. HealthTech has recently allocated funds for further development of this application of the Uniject device, with cofunding provided by the Bill & Melinda Gates Foundation.

Ultimate Goals and Objectives of HealthTech Project

Create a sustainable, commercial supply of gentamicin-Uniject.

[1] Uniject is a trademark of BD.

Status of Project as of September 2004

Unfortunately, work by PATH and Dolphin Laboratories Ltd. over the summer to identify a compatible formulation of gentamicin-Uniject did not yield positive results. Establishing compatibility is the critical path activity for gentamicin-Uniject during 2005. Therefore, formulation development work is being moved from Dolphin Laboratories to a contract laboratory with greater expertise in formulation problem investigation and resolution. This laboratory—also expected to be much more responsive than Dolphin—will establish: (1) if there is an underlying unresolvable issue of physical incompatability between gentamicin and the Uniject device or (2) if there are specific formulation and processing procedures that lead to an acceptably stable gentamicin-Uniject product. Dolphin's limited new product development experience has affected performance and has prompted the need to seek to identify manufacturer(s) that can: (1) supply field evaluation needs, and (2) provide ongoing commercial production and sale into the long term (these roles could potentially be filled by one firm). Given the uncertainty and evolving time frame of product availability, it will continue to be important for the PATH team to stay in close communication with Saving newborn Lives (SNL) and its collaborators about their planned Bangladesh field evaluation of gentamicin-Uniject.

Milestones expected in the past six months	Achievements and progress towards milestones
Given favorable results from compatibility testing, have Dolphin Laboratories conduct fill of gentamicin-Uniject products for stability testing and use in field evaluation.	Not completed due to unfavorable results from compatibility testing of the Uniject device with unbuffered gentamicin.
Negotiate scope of work and subcontract with SNL for implementation of field trial of gentamicin-Uniject in Bangladesh.	Revised scope of work was drafted but is currently on hold until product release dates are confirmed. The study design can then be reconfigured to work within a shortened time frame.
Appropriate concentration of buffered gentamicin solution will be identified.	Identified buffer/concentrations in May 2004. (Disappointing compatibility results followed.)
Gentamicin-Uniject products will be released for field trials.	Unfavorable results of stability testing precluded release of product.
Gentamicin-Uniject will be registered in Bangladesh.	On hold until product release dates are confirmed.
Ethical approval from PATH Human Subjects Protection Committee will be obtained for implementation of field trial research protocol.	Protocol and application revised in September. Currently on hold until product release dates are confirmed.

Problems encountered	Actions taken or plans to resolve
Buffered formulation failed compatibility testing.	Addressing the issue of gentamicin compatibility in the Uniject device is the critical activity for 2005. Formulation development work will be transferred to a contract R&D laboratory with greater expertise in formulation problem investigation and resolution—and with greater responsiveness and accountability—than Dolphin Laboratories.
Delay in availability of product will delay the start of field evaluation.	Regular communication with SNL collaborators (JHU and the International Centre for Diarrheal Disease Research—Bangladesh [ICDDR-B]) regarding status of product manufacture. If SNL project is extended for another year, coordination of field evaluation should still be possible.

Milestones expected in the next six months	Planned activities to reach those milestones
Development of a scope of work for formulation development with new laboratory facility. The scope of work will provide for further investigation of sodium citrate and alternate buffers for stabilizing gentamicin formulations and will include forced degradation studies.	Transfer formulation development activities from Dolphin Laboratories to a contract R&D laboratory with greater expertise in formulation problem investigation and resolution.
Technical due diligence assessment of new laboratory facility.	PATH technical staff to visit new R&D laboratory to determine capabilities and willingness as well as the time, cost, and level of external assistance necessary to achieve consistent production and controls of quality product in a timely fashion.
Identification and sourcing of bulk product.	Identify, source, and qualify three gentamicin bulk suppliers (three batches from each supplier will be tested). Based on these results, one or two bulk suppliers will be selected for use in continued product development.

Milestones expected in the next six months	Planned activities to reach those milestones
On an R&D bench level, fill Uniject with the most promising formulations and complete accelerated stability screening studies as per ICH guidelines.	Compatibility/stability testing of gentamicin-Uniject formulated with chosen buffer(s), under a range of different conditions. To be performed by contract R&D laboratory.
Recommendation for go/no-go decision for further pursuit of gentamicin-Uniject product.	Review of all pertinent data regarding formulation, compatibility, and stability. Final positive decision will result in production of field trial supply; final negative decision will be authorship of journal article detailing negative experience.
Liaise with SNL and its collaborators (JHU and the ICDDR-B) on an on-going basis.	Continue relationship with SNL and its collaborators to ensure that any timelines for gentamicin-Uniject production supports nesting the sub-study into the ongoing study of neonatal sepsis.
Once an assured supply of gentamicin-Uniject for field evaluation becomes available, prepare criteria for allocation of limited supply to potential, future field evaluations taking place in the 12-24 month time frame.	Collaborate with USAID to develop allocation criteria, seeking input from organizations that anticipate potential field work with gentamicin-Uniject.

Oxytocin in Uniject™ Devices

Health Need Addressed

Hemorrhage is the leading cause of maternal mortality and is a particular problem in home deliveries because the short response time makes referral impractical in most cases. The percentage of maternal deaths due to post partum hemorrhage (PPH) has been reported as 25% in sub-Saharan Africa, 27% in West Africa, and 45% in Indonesia. Annually, approximately 130,000 women are known to die due to hemorrhage during childbirth.[1] The use of oxytocin for routine management of the third stage of labor can significantly reduce the incidence of PPH. Active management of the third stage of labor (AMTSL), which includes routine use of a 10 IU dose of oxytocin given intramuscularly, is recommended by WHO for all institutional deliveries and home deliveries attended by a person with midwifery skills.[2]

HealthTech IV Solution and Potential Impact

A prefilled, nonreusable syringe, such as Uniject™[3] is thought to be the safest mechanism for delivering the life-saving benefits of oxytocin to women in peripheral health care settings and homes. This prefilled, easy-to-use, injection-ready format ensures that an accurate pre-measured dose is given in a nonreusable, sterile device with minimal preparation and minimum waste. Based on evaluations in Lombok, Indonesia, midwives found Oxytocin in Uniject (hereafter called "oxytocin-Uniject") to be safer and more convenient to use during home deliveries than traditional needle and syringe. This study, and results from an upcoming study in Vietnam, may indicate that oxytocin-Uniject can play a major role in facilitating adoption of AMTSL strategies, thus preventing maternal mortality due to hemorrhage.

Ultimate Goals and Objectives of HealthTech Project

Improve and ease adoption of AMTSL initiatives and therefore reduce PPH by engaging one or more pharmaceutical producers to supply oxytocin-Uniject commercially on an ongoing basis. Note that PATH has been supporting a minimal amount of work on this project to date with funding from another source. USAID funding for this project is starting October 1, 2004.

[1] http://www.mnh.jhpiego.org/best/pphactmng.asp (accessed 21Sep04)
[2] *Mother-baby package: Implementing safe motherhood in countries.* WHO/FHE/MSM/94.11, Geneva, 1994.
[3] Uniject is a trademark of BD.

Status of Project as of September 2004

Under funding from another donor, a supply of oxytocin-Uniject for field trial purposes was successfully produced in collaboration with Dolphin Laboratories Ltd. in Ahmedebad, India. Although product was available in a timely manner for use in a field trial in Vietnam, communication, timeliness, and quality assurance difficulties with Dolphin Laboratories persist. Because of this, alternative short-term suppliers of Oxytocin-Uniject will be sought during the upcoming year.

Milestones expected in the past six months	Achievements and progress towards milestones
Produce oxytocin-Uniject in sufficient quantities for field evaluation.	Production of oxytocin-Uniject (July-September 2004) by Dolphin Laboratories Ltd of India. Product supplied to field trial in Vietnam (funded by Averting Maternal Death & Disability [AMDD]).
Stability evaluation of the industrial batch to be used in field trials.	One month stability study results at 4°C, 25°C, 30°C and 40°C show that product could remain stable for up to 3 years at 4°C and more than 200 days at 30°C–this is an ongoing study and reports will be issued on a timely basis throughout.
Stability evaluation (of the January 2004 batch) at different environmental conditions.	A 15-week stability study completed at 30ºC (July 2004).

Problems encountered	Actions taken or plans to resolve
Lack of timely response from Dolphin Laboratories regarding data monitoring requests.	Improved oversight of and enhanced communication with Dolphin Laboratories via PATH New Delhi office staff. Investigation of alternative short-term supplier of oxytocin-Uniject product.

Milestones expected in the next six months (under HealthTech funding)	Planned activities to reach those milestones
Decision on short-term supplier plan.	Investigate and determine if Dolphin Laboratories can satisfy the next round of field evaluation demands (decision by the end of 2004). Investigate if a pharmaceutical producer with existing Uniject device filling capacity could collaborate to fill and package product for the next round of field evaluation demands (assess by end of 2004).
If not Dolphin Laboratories, engage alternative interim supplier.	Additional field study supply available the end of 2005 to the first half of 2006 *if* alternative, interim supplier is chosen.
If Dolphin, undertake technical assistance necessary to improve their reliability and quality as an oxytocin-Uniject supplier.	Additional field study supply available *if* Dolphin Laboratories is judged worthy of more effort.
Participate in the Prevention of Postpartum Hemorrhage Initiative (POPPHI) uterotonic supplies working group.	Draft policy brief about supply issues for all uterotonic drugs (oxytocin, oxytocin-Uniject, misoprostol) for review and approval by POPPHI.
If sufficient funding available, identify suitable laboratory partner to conduct formulation investigation.	Identify and collaborate with suitable laboratory partner to plan and, if so determined, begin testing.
Complete evaluation of supply allocation criteria.	Develop criteria for allocating limited interim supply of oxytocin-Uniject for use in upcoming field evaluations. Monitor ongoing community-based studies designed to reduce maternal mortality.
Develop timetables of oxytocin-Uniject availability for field evaluators, concurrent with development of short-term supplier.	Coordinate interim supply of oxytocin-Uniject for field evaluations, including transfers from interim producer to appropriate programs.

Introduction of Injectable Contraceptives in the Uniject™ Device

Health Need Addressed

Injectable contraceptives are becoming increasingly popular around the globe as women search for safe, highly effective, reversible methods of contraception that do not require compliance with a daily regimen. Depot medroxyprogesterone acetate (DMPA) is administered by injection once every three months, making it highly convenient. Cyclofem®[1] (also known as Lunelle and CycloProvera) injectable contraceptive is administered by injection every month and is formulated to allow women to have more normal menstrual cycles—an advantage in many cultures. Currently, international development and family planning agencies purchase over 25 million doses of DMPA injectable contraceptives annually for distribution to family planning programs throughout developing countries. Approximately seven million doses of Cyclofem injectable contraceptives were sold in the year 2000.

International development and family planning agencies and recipient governments are continually looking for feasible and affordable methods to reduce unsafe injection practices that can lead to the spread of bloodborne diseases. Provision of one sterile needle and syringe with every dose of injectable contraceptive is the current standard. However, there is a risk with disposable syringes that they will be reused. Auto-disable (AD) syringes prevent reuse, but like disposable syringes they can be diverted to other uses during the distribution process. The Uniject™[2] prefill injection device has distinct advantages in terms of both safety and procurement.

HealthTech IV Solution and Potential Impact

A decade ago, prefilled syringes were too costly for use in public-sector health programs, and no prefilled syringe on the market offered an AD feature. Under the HealthTech project, PATH was able to develop the Uniject device, a proprietary, prefilled, AD injection system. The Uniject device prevents reuse, simplifies matching of syringes and supplies, ensures dose accuracy, and is so simple to use that injection at home by the patient or a family member is feasible. Now the device is being considered for use filled with injectable contraceptives. With funding from the USAID Office of Population, PATH has been working for a number of years with the dominant international supplier of DMPA injectable contraceptive to evaluate potential use of Uniject devices. This company was Pharmacia until it merged with Pfizer in April 2003. PATH has also worked with Aplicaciones Farmacéuticas, a Mexican pharmaceutical company which has developed but not yet launched a version of its once-a-month injectable contraceptive, Cyclofem, in Uniject devices.

[1] Cyclofem is a registered trademark of the Concept Foundation.
[2] Uniject is a trademark of BD.

Ultimate Goals and Objectives of HealthTech Project

- To increase the safety, acceptance, and reach of DMPA injectable contraceptives in family planning programs.
- To enable innovative new family planning program options, such as home injection and outreach.

Status of Project as of September 2004

As noted in the previous HealthTech semiannual report, PATH's activities are dependent on the pace and progress of Pfizer's technical development and the Pfizer-BD Uniject supply agreement negotiation. Progress has been made the past six months,. BD, Pfizer, and PATH met in September to consider aspects of the BD-Pfizer supply agreement that impact developing-country availability of injectable contraceptives in Uniject. We learned in that meeting that Pfizer's new-DMPA in Uniject project has progressed through many layers of the Pfizer management approval system for investment in new products. The Pfizer Uniject team now has approval to procure and install one full set of production-scale Uniject filling and packaging equipment. They will use the equipment to produce three large-scale pilot lots of new-DMPA in Uniject. While these steps are still seen within Pfizer as "final feasibility" exercises, they represent an investment by Pfizer in the low million-dollar range. The large-scale pilot lot production of new-DMPA in Uniject will serve multiple purposes at Pfizer:

- Pfizer regulatory specialists have some concern about meeting the latest USFDA aseptic injectable manufacturing standards with the current generation Uniject filling machine—production of these full-scale pilot lots will be their definitive evaluation of this possible issue.
- Unless an insurmountable manufacturing issue arises, the three production lots will create product so Pfizer can conduct the definitive stability studies using "three industrial batches" that are necessary for USFDA registration of new-DMPA in Uniject.
- The definitive stability studies will require only a fraction of the complete production runs, and Pfizer has indicated that the excess new-DMPA in Uniject will be made available to USAID for potential use in clinical trials.

Milestones expected in the past six months	Achievements and progress towards milestones
Pfizer to initiate negotiations with BD for a long-term supply agreement for Uniject devices.	BD, PATH, and Pfizer agreed to preliminary structure of supply agreement (September 2004).
Propose a USAID/PATH-facilitated injectable contraceptive stakeholders meeting to gather input and buy-in on a strategy and position regarding Pfizer's anticipated demands for exclusive use of the Uniject device for injectable contraceptives	PATH and USAID determined that such a meeting was unnecessary.

Problems encountered	Actions taken or plans to resolve
While Pfizer has now begun negotiations with BD for Uniject supply, the pace of the firm's progress on DMPA-Uniject remains deliberate.	PATH will continue to keep in contact.

Milestones expected in the next six months	Planned activities to reach those milestones
Continue to encourage progress by BD and Pfizer towards finalizing a Uniject supply agreement, so as to wrap up PATH involvement in the negotiation.	PATH review of BD-Pfizer supply agreement dependent on BD-Pfizer pace. At latest we expect final BD-Pfizer supply agreement to be signed by the end of 2004.
Complete collection of data needed to update the background paper on volumes and trends in supply of injectable contraceptives to international donor agencies for distribution in developing countries.	Collect data from international donors including USAID, DFID, UNFPA, and IPPF on current procurement of injectable contraceptives for use in developing-country programs. Complete data collection by early 2005.

Draft an updated timeline/decision-point diagram to identify and map key milestones and decision points in Pfizer's new-DMPA program (their work to develop, register, and scale up production for new-DMPA in Uniject.) Emphasis is on identifying any key remaining decision points for Pfizer and the likely timing of availability of supplies of new-DMPA in Uniject to USAID.	Initial, draft diagram will be completed by the end of 2004.
Hold a collaborator meeting between USAID, PATH, Pfizer, and BD to finalize the timeline/decision-point diagram noted above.	The collaborator meeting between USAID, PATH, Pfizer, and BD will take place early next year.
Clarify needs for any training and information materials—during 2005—to support potential clinical and field evaluations of new-DMPA in Uniject.	Once availability of new-DMPA in Uniject is known—as it relates to USAID-initiated clinical evaluations—meet with Office of Population (and possibly clinical collaborators) to determine needs. A schedule for completion of materials will be agreed upon at that time.

Diagnostic Technologies

Retinol Binding Protein Enzyme Immunoassay (RBP-EIA)

Health Need Addressed

Micronutrient malnutrition has emerged as one of the greatest public health concerns in the world today. Almost one third of children in developing countries are affected to some degree by vitamin A deficiency (VAD), which impairs their growth, development, vision, and immune function (including resistance to disease), and in extreme cases leads to blindness and death.[1, 2, 3]

A body of knowledge and experience exists that effectively addresses VAD through both short-term and long-term interventions. Global efforts have promoted capsule supplementation, food fortification, nutrition education, and the so-called food-based strategies to combat VAD. However, the targeting and implementation of effective interventions requires accurate and timely data. Generating information on VAD at a country and subnational level has been hampered by technology constraints. The lack of affordable, valid, and reliable screening methods has made it difficult and expensive to conduct badly needed vitamin A assessments. The development and introduction of the retinol binding protein-enzyme immunoassay (RBP-EIA) to assess VAD alleviates this constraint by generating prevalence data and information to promote the planning, implementation, and evaluation of vitamin A interventions to improve child health and nutrition.

HealthTech IV Solution and Potential Impact

The RBP-EIA is a competitive assay, which detects and quantifies retinol binding protein in human serum. The test uses purified human RBP adsorbed to microtest strip wells to compete with natural RBP found in serum. The test results for 96 determinations are available in as few as 35 to 40 minutes after the start of the assay; however, it is strongly recommended that all samples, including calibrators, be performed in duplicate. Therefore, the kit provides a total of 48 results. The RBP-EIA is designed to access and monitor the vitamin A status in populations. While the results for the assay are quantitative, it should not be considered a diagnostic test for detection of VAD in individual patients, but rather, as a research and epidemiological surveillance tool to be used at a population level.

This technology addresses USAID's strategic objective to increase the use of key child health and nutrition interventions (SSO3). It does this by improving the quality and availability of key screening services (IR 3.4), improving preventive behaviors related to child health and

[1] UN ACC/SCN (United Nations Administrative Committee on Coordination/ Subcommittee on Nutrition). Third report on the world nutrition situation. ACC/SCN, Geneva, 1997.
[2] WHO (World Health Organization), Global prevalence of vitamin A deficiency: micronutrient deficiency information system. WHO MDIS Working Paper # 2. WHO, Geneva, 1995.
[3] Sommer A and West KP. Vitamin A deficiency: health, survival, and vision. New York, NY and Oxford, UK: Oxford University Press, 1996.

nutrition (IR 3.3), and providing information to improve policies and increase global, national, and local resources for appropriate child health interventions (IR 3.2).

The RBP-EIA offers a rapid, inexpensive, and quantitative tool for determining vitamin A status at the population level. Vitamin A status is currently being determined by "gold standard" HPLC methodologies that are expensive and require significant investments in training and time to carry out. The RBP-EIA test developed at PATH is simple and requires a relatively small amount of specimen. It reduces reliance on centralized laboratory facilities in developing countries and saves time and money by eliminating the need to transport specimens to a developed country for analysis using overly sophisticated and costly tests such as HPLC. It provides a more cost-effective tool for the monitoring and recognition of VAD in targeted populations, will assist surveillance units in the field with the assessment of VAD status at the population level, and reduces the time between assessment and implementation of interventions to address VAD. We expect that the RBP-EIA will facilitate the ease of conducting vitamin A field assessments and increase the number of countries that conduct prevalence surveys to assess VAD, especially in countries where they have not yet been performed, but where the need may be the greatest.

Ultimate Goals and Objectives of HealthTech Project

Our goal is to enhance the reliability and ease of VAD assessment and decrease the associated cost. Our objectives are to:

- Improve the consistency of the results of vitamin A assessment, including ease of specimen analysis and interpretation.
- Improve the reliability of VAD estimates.

Status of Project as of September 2004

Earlier this year, the test was licensed to a private-sector company. Production lots have been validated and are ready for commercialization. A strategy for a controlled commercial introduction of the product has been developed between PATH and the commercial partner to ensure the informed selection and appropriate use of the test. An evaluation study conducted in Thailand was successfully completed and results will be presented at the International Vitamin A Consultative Group (IVACG) meetings in Peru in November 2004. With the results of the study, we expect to build consensus from the broader vitamin A community on the utility of the test.

Milestones expected in the past six months	Achievements and progress towards milestones
Conduct collaborative operational field study with the Micronutrient Operational Strategies and Technologies Project (MOST) and the University of Washington.	Study conducted with University of Washington and MOST; participation in Thailand was successfully completed in September 2004. Results will be presented at IVACG in November 2004 in Peru.
Work with Scimedx to make the RBP-EIA commercially available in 2005 by monitoring quality, introducing Scimedx to potential users, and developing a promotion strategy.	Quality control evaluation has been completed; test to be manufactured for commercial sale by Scimedx.
Ensure the appropriate use of the test by developing and testing job aids in support of its field use, providing technical support to early adopters, and obtaining end-user feedback through a questionnaire.	The development of job aids to support the collection, handling, and storing of samples has been drafted. The development of job aids to support the use of the RBP-EIA in the field has been postponed and is planned for the first half of 2005.
Meet with key donors of existing micronutrient programs to foster informed selection of the test, publish journal articles, develop briefing materials, participate in international nutrition meetings, and conduct test demonstrations.	Delayed until next reporting period. See below.

Problems encountered	Actions taken or plans to resolve
None.	

Milestones expected in the next six months	Planned activities to reach those milestones
Complete data analysis of dried blood spots (DBS) stability study conducted in Tanzania.	Data analysis completed and report of results drafted.
Meet with key donors of existing micronutrient programs to foster informed selection of the test, publish journal articles, develop briefing materials, participate in international nutrition meetings, and conduct test demonstrations.	Results from the Thailand study will be presented at IVACG along with a presentation on the RBP-EIA and the RBP-immunochromatographic strip (ICS) that was developed under funding from Centers for Disease Control and Prevention (CDC).

Senegal sample analysis for retinol completed by CDC as a result of multiple problems with the original retinol analysis. Complete analysis of the RBP from serum collected for a micronutrient intervention conducted in Senegal in conjunction with UC Davis, the University of Dakar, and Micronutrient Initiative.	Analysis of data from micronutrient intervention research project being conducted in Senegal in conjunction with UC Davis, the University of Dakar, and Micronutrient Initiative complete. Report of results drafted.
Job aids developed and field-tested in support of field use of the RBP-EIA. End-user feedback obtained and incorporated into the RBP-EIA and supporting materials.	Develop new training materials, such as job aids and training CD. Specifically, develop a CD ROM and PowerPoint presentations that provides programmatic guidelines for the RBP-EIA test. Test and revise existing and new training materials through end-user benchmarking. Finalize job aid for sample collection, handling and storage. Obtain end-user feedback through a questionnaire.
Candidate “early adopters” are selected and provided with RBP-EIA tests and Q&A technical support at no cost to gain exposure for the test, build a market, and demonstrate the technology. Quality control activities are implemented to ensure that both retinol and RBP assessments are precise and accurate.	Purchase tests from Scimedx to support early adopters. Screen interested users based on specified selection criteria to ensure that the RBP-EIA is being used to assess VAD in populations. Work with Scimedx to make the RBP-EIA commercially available in 2005 by monitoring quality and introducing Scimedx to potential users. Work with Scimedx to establish system for complaint resolution and feedback mechanism to PATH

RBP-EIA introduced to key stakeholders and the broader consumer audience. Communication tools developed and introduced to describe and promote the RBP-EIA test.	Develop advocacy materials for RBP-EIA for all stakeholder groups to introduce the technology as a "new approach to vitamin A assessment." Develop technical bulletin with Scimedx. Create communication tools describing the RBP-EIA and its potential use. Publish validation results and share those results with the scientific community and other interested groups. Contribute to PATH Today and Roche Vitamin A Sight and Life newsletters. Organize a series of meetings with key stakeholders who support and conduct vitamin A interventions or research to introduce potential users to benefits, ease, and applications of new technology. Work closely with USAID's nutrition unit as a partner in this activity, where PATH takes the lead in organizing and conducting these meetings.

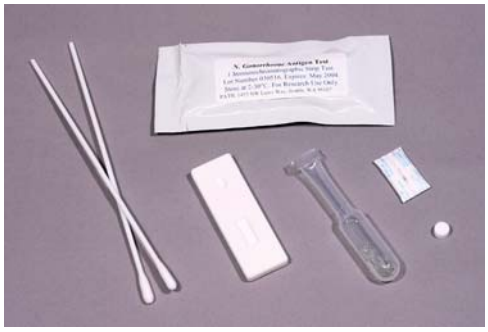
Immunochromatographic Strip Test for Gonorrhea

Health Need Addressed

Despite long-standing, global public health efforts to control sexually transmitted diseases (STDs), infections caused by *Neisseria gonorrhoeae* still occur in epidemic proportions in the developing-world and in specific regions of the United States. For effective control of gonorrhea (GC), STD control programs must offer early and accurate diagnosis of symptomatic infection and identification of invasive, complicated, or asymptomatic infections. Control of STDs is also considered to be an essential component in the control of HIV/AIDS transmission.

HealthTech IV Solution and Potential Impact

The immunochromatographic strip (ICS) test for diagnosis of GC, developed under HealthTech III and IV, utilizes relatively inexpensive, off-the-shelf components and is formatted to identify L7/L12, a specific gonoccocal antigen, directly from clinical specimens. The strips are stable at ambient temperatures when packaged appropriately. This simple, rapid test will allow testing to be performed on direct clinical specimens from patients in rural or smaller clinics, regional hospitals, and STD clinics in the developing-world, or in other resource-limited settings. Results can be returned within one hour, thereby allowing effective patient follow-up, additional counseling, and prescription of therapeutic drugs, if needed. Epidemiological surveillance teams in the field may also use the test to gather baseline data or to assess the effect of public health interventions.



Test kit for diagnosis of GC

Ultimate Goals and Objectives of HealthTech Project

- Commercial availability of rapid gonorrhea test for use in developing countries.
- Published data supporting the utility of this test in the developing-world.
- Endorsement of the test by WHO.

Status of Project as of September 2004

PATH is currently at a major turning point in the development and introduction of the GC ICS test, which has already been successfully validated in one field evaluation. We have completed negotiation of a licensing agreement for a technology transfer to a well-respected commercial manufacturer and are in the process of validating their production lots. A large volume of test kits were produced and used in the WHO multi site trial. An additional study site will be identified for field evaluation and introduction in the coming months.

Milestones expected in the past six months	Achievements and progress towards milestones
Licensing agreement and technology transfer completed.	Technology transfer agreement was signed by PATH and our commercial partner. Supply agreement was also successfully negotiated and is under final review by all parties. Commercial partner, who claims to have improved the test since taking on the project, is sending prototypes to PATH for evaluation. An on-site visit to the commercial partner is planned for later this year in order to evaluate progress.
Finalize collaborations with introduction study partners and implement studies in developing countries.	Identified interested collaborators and began protocol development for several sites in India.
Produce and supply a large batch of prototype tests to WHO for a comparative study in Benin.	Test batch was produced and sent to Benin for participation in the WHO study. Results were disappointing.

Problems encountered	Actions taken or plans to resolve
Licensing agreement and technology transfer process took longer than expected.	We held conference calls and email correspondences with the party holding intellectual property needed for the test and with our transfer recipient to move the process forward.
Production of tests was difficult in Seattle due to high humidity, so the supply of tests to WHO was delayed.	The GC project and other ICS test projects contributed to purchasing a dry room for test production. It is up and running well; tests were produced and shipped to WHO in the last month.

Milestones expected in the next six months	Planned activities to reach those milestones
Collaboration with our technology transfer partner to improve the performance of the test.	PATH staff will visit the technology transfer sit–Orchid Diagnostics in India–to conduct experiments with a new gold conjugation technique and other biochemical and physical additions that may improve the sensitivity of the test.
Increase coverage of use of the GC test by identifying additional commercial partners outside of the current partner's area of distribution.	Second commercial partner, preferably in the western hemisphere, identified for possible technology transfer.
Collaborate with developing-country partner on validation/introduction study.	We will develop a study protocol, obtain Human Subjects Protection Committee approval, initiate recruitment of study participants in early 2005 and implement the study by the end of 2005.

Immunochromatographic Strip Test for Chlamydia

Health Need Addressed

Accurate diagnosis and control of STDs continues to be a challenge for health care providers in many developing countries. Although there are many simple and rapid tests available for the diagnosis of *Chlamydia trachomatis* (CT) infection, the sensitivity of many are low, and most, if not all, are too expensive for use in developing countries. The development of a rapid immunochromatographic strip (ICS) test for Chlamydia that is sufficiently sensitive, specific, rapid, and affordable would be an extremely valuable tool.

HealthTech IV Solution and Potential Impact

The ICS test for Chlamydia, developed under HealthTech III, utilizes relatively inexpensive, off-the-shelf components and is formatted to identify a Chlamydia-specific antigen obtained directly from clinical specimens. The strips are stable at ambient temperatures if packaged appropriately. This simple, rapid test will allow testing to be performed on direct clinical specimens from patients at the point of care in rural or smaller clinics, hospitals in the developing-world, or other resource-limited settings. Results can be returned within one hour, thereby allowing effective patient follow-up, additional counseling, and the prescribing of appropriate therapeutic drugs if needed. Epidemiological surveillance teams in the field may also use the test to gather baseline data or to assess the effect of public health interventions.

Ultimate Goals and Objectives of HealthTech Project

- Commercial availability of rapid Chlamydia test for use in developing countries.
- Published data supporting the utility of this test in the developing-world.
- Endorsement of the test by WHO.

Status of Project as of September 2004

Further development of the CT ICS test has slowed awaiting clinical samples. Sample collection is currently underway in collaboration with Planned Parenthood Mar Monte (PPMM) in California. To date approximately 50% of the positive samples required to complete the study have been collected. This is sufficient to begin evaluation of the test in order to verify the clinical utility of the antibody selected for use in the assay. From the analysis of this subsample of specimens we have demonstrated 60% sensitivity and 98% specificity as compared to Strand Displacement Amplification (SDA). With these promising results, additional sites will be identified to obtain more samples for further evaluation of the test. If the test continues to perform well, we will move forward with evaluations and commercialization; but if the test does not perform well, discussions with USAID will be necessary to decide whether to continue the project.

Milestones expected in the past six months	Achievements and progress towards milestones
Retrospective evaluation of clinical samples and assay verification to begin once the final prototype device is determined and specimens are available.	Collection of clinical samples has been slower than anticipated. Currently 50% of the required samples have been collected. Using those samples we have demonstrated 60% sensitivity and 98% specificity as compared to SDA.
Development of the CT ICS test to continue once the assay reagents and components are verified with the retrospective evaluation.	Verification of the assay has taken place; however, more work is needed to increase the sensitivity of the assay. Due to the slow rate of sample collection to date, we feel that it will become necessary to find additional sources of samples for this work.
Documents describing the processes and procedures for manufacturing the assay and its components (e.g., standard operating procedures) to be drafted and refined as the product is developed.	The documents have not been drafted as the prototype devices have not yet been made or tested using the PPMM specimens.

Problems encountered	Actions taken or plans to resolve
Collection of clinical specimens continues to be slower than anticipated.	In order to widen the area of patient enrollment for this study, PPMM has added several clinical sites within their region. Collection rates and CT prevalence are therefore anticipated to increase. The situation continues to be monitored closely. We have begun looking for alternative sites to collect specimens for testing in conjunction with PPMM.

Milestones expected in the next six months	Planned activities to reach those milestones
Retrospective evaluation of clinical samples and assay verification has been completed on the two-step extraction system prototypes but remains to be done using the single-step extraction version.	Produce prototypes and evaluate them using samples currently on hand from PPMM. Identify an additional field site and collaborator for the collection of clinical samples to evaluation the CT test using the single-step extraction process. Draft protocol for the collection of clinical samples, and develop agreement between collaborating organization. Obtain appropriate IRB approvals for conducting the study.
Development of the CT ICS test to continue once the assay reagents and components are verified with the retrospective evaluation.	Verify the CT ICS prototype using PPMM samples. From those results, determine if the antibody selected is indeed providing good sensitivity and specificity.
Documents describing the processes and procedures for manufacturing the assay and its components (e.g., standard operating procedures) to be drafted and refined as the product is developed.	Once we have determined that the test and its components perform adequately using specimens from the PPMM study, we will then begin drafting procedures for manufacturing the assay and its components (e.g., standard operating procedures).
Investigate signal enhancement systems to improve the assays sensitivity.	Work with consultants and collaborators to identify and evaluate alternative methods to enhance the CT assay's signal system (asymmetric colloidal gold, silver enhancement, and others).

Rapid Diagnostics for Tuberculosis

Health Need Addressed

Tuberculosis (TB), the disease produced by the bacterium *Mycobacterium tuberculosis*, continues to cause significant morbidity and mortality worldwide. Recently, the increasing incidence of TB—particularly in the developing-world—has been associated with human immunodeficiency virus (HIV) infection, the emergence of multiple drug-resistant strains, and the breakdown of preexisting screening programs. Globally, TB is already the leading cause of death among people with AIDS, accounting for about 40% of fatalities in Africa. While worldwide reporting reflects incomplete data, it is estimated that globally as many as three to four million deaths can be attributed to TB each year. Astonishingly, this figure exceeds the estimate for malaria or acute respiratory infections and ranks TB as one of the most important infectious disease problems today. The available data indicate that 95% of the clinical cases and 98% of the deaths attributable to TB occur in the developing-world.

The general consensus is that the top priority for TB-control programs should be active case detection, confirmation of infection, and therapy for all infectious cases in both low- and high-prevalence areas. Since 1996, WHO has promoted the Directly Observed Therapy Short Course (DOTS) strategy for TB control, one aspect of which is case detection through sputum smear microscopy of TB suspects. The emphasis on TB diagnosis by sputum smear microscopy is, however, problematic. The method is simple and relatively inexpensive but requires quality microscopes, experienced microscopists, and exacting quality control. The specificity of smear microscopy has been reported to be as high as 99.2%, but reports of sensitivity range from 40% to 60% for a combination of three examinations and may be as low as 20% to 25% in high HIV sero-prevalent populations (personal communication, Michael Iademarco, CDC).

In developing countries, diagnostic sensitivity may be improved by sputum culture. However, a sputum culture takes weeks to yield results and requires dedicated equipment and technical expertise. Long delays can result in the patient being treated empirically and inappropriately, and the cost of some of the current culture systems may also be beyond what many control programs in resource-poor countries can afford. Recently, several new diagnostic methods for TB have been developed, including nucleic acid detection and amplification techniques. Although they provide advantages in terms of sensitivity, these methods are still too technically complex and expensive for use in most developing-country settings.

HealthTech IV Solution and Potential Impact

Serodiagnostic technology offers the potential for development of rapid, inexpensive tests for TB. They can be fairly simple to use, formatted as high- (e.g., ELISA-based assays) or low-volume assays (e.g., immunochromatographic strip tests), and can be relatively inexpensive. There have been efforts to develop TB serodiagnostic tests for many years, but early tests had unacceptably low specificity. High test specificity is required because a false

positive result can commit the patient to a long course of inappropriate therapy, with risk of stigma, high costs of antibiotics, and the potential for side effects.

For the developing-world, inexpensive and less complex serodiagnostic tests can be developed in simple dipstick, strip, or particle agglutination formats, which can be performed in clinics with lower patient volumes. These could be used at the peripheral or district health care level to fortify syndromic diagnosis of TB in sputum-positive patients and to detect suspected cases of sputum-negative or extra-pulmonary TB. This would be especially effective in specialty applications (e.g., testing of HIV-positive persons), since the clinical signs and symptoms of TB are often atypical, and skin test anergy may be present.
The development of a TB immunochromatographic strip (ICS) test could provide an alternative diagnostic tool to supplement or replace microscopic diagnosis of TB-positive sputum smears or identify suspected cases of TB-negative sputum smears or extra pulmonary TB infection and therefore will:

- Extend or enhance immediate or same-day return of results in intermediate to peripheral hospitals and clinics to allow appropriate therapy to be administered.
- Provide a back-up tool to microscopic examination of stained sputum smears for use in central or specialty clinics where high-volume diagnosis is currently performed well.
- Potentially reduce testing costs through technology transfer for commercial manufacturing in the developing-world.

Ultimate Goals and Objectives of HealthTech Project

- To develop an accurate and simple serodiagnostic test for TB, which is affordable to populations in the developing-world.
- To understand the need and market for rapid diagnostics for TB in order to make informed decisions about investments in development of tests.

Status of Project as of September 2004

HealthTech has developed and field tested one version of a rapid test–an ICS test. We are also actively searching for new approaches and platforms for tests to improve rapid detection of TB, especially in regions with high HIV prevalence, and are initiating a market study.

Milestones expected in the past six months	Achievements and progress towards milestones
Publication of results of Botswana study of rapid diagnostics for TB.	"Tuberculosis Serodiagnosis in a Predominantly HIV-Infected Population of Hospitalized Patients with Cough, Botswana, 2002" (Attachment 2), was published in the July 2004 issue of *Clinical Infectious Diseases*. None of the tests, including the HealthTech ICS test, performed very well on this population with a high prevalence of HIV.
Submission of a manuscript to a peer-reviewed journal summarizing our experience with rapid tests employing serological diagnosis of TB. This manuscript will detail the results of the field trials, the shortcomings of serological diagnosis using our antigen/antibody targets in an ICS format, and a description of new technologies, which may improve TB diagnosis at the point of care.	Currently writing the initial draft of the manuscript.
Assemble tests for the evaluation of the TB ICS test with archived samples from pediatric populations in Botswana.	Tests were assembled and delivered to Botswana where they are currently being used by our CDC partners.

Problems encountered	Actions taken or plans to resolve
Procuring antigens from commercial manufacturers. The primary supplier of antigens for the HealthTech ICS test recently went out of business.	We received a final, limited supply of antigens from our suppliers after negotiations with the now defunct company and others.
Due to the poor results in the field evaluation in Botswana on adult samples, a scope of work for further development of the TB ICS test has yet to be determined	PATH is engaging in collaborations with two industry partners who have promising new platforms and technologies for TB diagnosis.

Milestones expected in the next six months	Planned activities to reach those milestones
An understanding of the demand for rapid TB diagnostics in the public sector, taking into account the geographic, demographic, and health system variations present in five countries in the developing-world.	Collect and analyze individual-and group-level data from five countries that will inform our understanding of market size and possible obstacles to adoption of new diagnostics.
Develop and conduct a market analysis that will study the economic and public health impact of the introduction and uptake of new diagnostic tests. The study is planned to take place in 5 countries.	Develop and run simulation models for uptake of new diagnostics. Present to the Gates Foundation Forum on Global Diagnostics. Prepare a manuscript describing these activities for submission to a peer-reviewed journal.
Formal collaboration with partner for the development of a new rapid assay approach to TB diagnosis that employs macrophage replication as a mechanism for signal detection in sputum samples.	Establish a scope of work and collaboration agreement for preliminary experiments with Microphage, a private-sector company that has successfully demonstrated a phage-based ICS for other pathogens.
Proof of principle of a TB diagnostic using phage replication and lateral flow technologies.	Complete experiments that demonstrate proof of principle for a TB-phage-ICS.
Identification and early development of another new serodiagnostic test for TB. Report on results from new experiments.	Collaborate with Foundation for Innovative and New Diagnostics (FIND) to develop new experiments to evaluate antigen targets for use in a serologic test. Completion of preliminary experiments on the feasibility of these targets.
Recommendations about the future of serodiagnostic tests for TB.	Conduct a meeting between FIND and PATH to determine next steps and raise funds, if the recommendation is to proceed with further development and advancement of serodiagnostic tests.

Diagnostics for Surveillance

Health Need Addressed

Measles is a highly infectious, acute viral illness that is a leading cause of childhood death, malnutrition, diarrhea, mental retardation, visual and hearing impairment, and immune suppression in many African countries. Despite the worldwide decline in the incidence of measles cases, the disease remains a major cause of mortality and morbidity, accounting for over 800,000 deaths annually[1,2] with >50% occurring in Africa.[3] WHO/AFRO has recommended case-based surveillance in conjunction with immunization as a means of controlling and preventing measles outbreaks.[4]

Currently, the confirmation of suspected cases of measles is from serum samples using an enzyme immunoassay (EIA) as mandated by the World Health Organization.[5] Measles diagnosis from serum requires that venipuncture be performed, a process that involves the use of syringe and needle, centrifugation of the blood sample to separate the serum, cold chain for shipment of the separated serum, and the handling and disposal of infectious waste. These factors increase the costs associated with measles diagnosis, costs that are already a financial strain in resource-poor countries. An alternative to serum is the dried blood spot (DBS), which the WHO has identified as an appropriate sample for the detection of measles-specific IgM.[5]

HealthTech IV Solution and Potential Impact

The use of DBS instead of sera can potentially reduce the costs and infrastructure requirements associated with measles detection and surveillance. Demonstration of DBS samples as an economical, convenient, and equally effective alternative to sera for the detection of measles-specific IgM can give further support to WHO and country surveillance programs for the use of this sampling technique for measles detection. Moreover, because of the convenience of sample collection, transport, and storage of the filter paper cards, incorporation of the DBS sampling method in measles surveillance can conceivably lead to an increase in coverage of suspected measles cases. PATH is collaborating with Ghana's Public Health Reference Laboratory (PHRL), National Surveillance Unit (NSU), and Health Research Unit (HRU), as well as the USAID-supported Partners for Health Reform Plus (PHR+) project to evaluate the impact of DBS sampling technique on the Ghanian Integrated Disease Surveillance and Response (IDSR) measles surveillance system. The operational

[1] de Quadros CA. Can measles be eradicated globally? Public health reviews. *Bulletin World Health Organization*. 2004; 82(2):134-138.
[2] Bellini WJ, Helfand RF. The challenges and strategies for laboratory diagnosis of measles in an international setting. *Journal of Infectious Disease*. 2003; 187(S1):S283-S290.
[3] El Mubarak HS, Yuksel S, Mustafa OM, et al. Surveillance of measles in the Sudan using filter paper blood samples. *Journal of Medical Virology*. 2004; 73:624-630.
[4] World Health Organization/Regional Office for Africa (WHO/AFRO), Vaccine Preventable Disease Unit, WHO/African Region. Measles surveillance in the African Region. *Vaccine Preventable Diseases Bulletin*. 2003; 35:1-3.
[5] World Health Organization (WHO), Department of Vaccines and Biologicals, Geneva. Research related to measles control and elimination. *Measles Bulletin*. 2000; 3:2.

success of this study may facilitate a wider application of DBS as a preferred collection method for other infectious diseases.

Ultimate Goals and Objectives of HealthTech Project

To evaluate the operational feasibility of DBS samples for measles surveillance in a developing-country, the following objectives have been identified:

- Collaborate with the Ghanaian MOH to design and prepare for technical and operational assessment of DBS in current measles control activities.
- Assist PHRL with training for collection and transport of DBS for measles testing using an EIA.
- Collect quantitative and qualitative data on costs, benefits, utility, and performance of DBS for measles case confirmation in existing surveillance system.
- Evaluate the technical performance of DBS collected from finger-stick blood to detect measles-specific IgM with a commercially available EIA.
- Write up and disseminate study results with assistance of PHRL, NSU, and HRU.

Status of Project as of September 2004

In June-July of 2004 a visit was made to Ghana to determine the MOH's interest and ability to collaborate on an evaluation of the DBS as an alternative measles surveillance method. Discussions included laboratory, programmatic, MOH, and health research personnel. Overall support and interest in this project was expressed. Current surveillance protocols and data were collected and the local WHO disease officers informed of potential research activities. Interest, relevance, and participation have been established for investigating the use of DBS as an alternative measles surveillance method. However pending funding, activities are currently on hold.

Milestones expected in the past six months	Achievements and progress towards milestones
Operations research design visit to Ghana completed. During this visit decisions will be made on the type of test to be used, study population, operations parameters to be studied, implementation plan, and timeline.	Visit achieved June 25 to July 8, 2004. Consensus was reached about the overall objective of a study.
Study protocol drafted for Ghana MOH review, and preparations begun for implementation.	Protocol writing is on hold pending funding discussions.

Problems encountered	Actions taken or plans to resolve
Scheduling difficulties with Ghana MOH and PATH staff.	Study will be rescheduled once funding is identified.
Uncertain resources to define scope of project and move forward. The balance remaining in the budget provided by SO5 originally is insufficient for the full scope of the study.	Discussions pending. PATH will propose a budget to USAID for additional funding to carry out the full scope of the study.

Milestones expected in the next six months	Planned activities to reach those milestones
All arrangements formalized for study to be completed by December 2005.	Secure funds and staff time to prepare study design and protocol.
Training plan and materials developed by end of December 2004.	Prepare training plan and materials.
Specimen and data collection SOPs and forms produced by February 2005.	Prepare laboratory SOP and data collection forms.
Initiation of study by March 2005, if further funds can be identified.	Conduct field visit and training to launch study.

Rapid Diagnostic Tests Web Site

Health Need Addressed

Program planners, managers, and laboratory staff need clear, well-documented information about choices of available diagnostic tests in order to make informed decisions, particularly when resources are limited. Because rapid diagnostic tests are a relatively new group of technologies, comprehensive information is difficult to find. PATH regularly receives inquiries about the availability and appropriate uses of a wide range of rapid diagnostic tests.

HealthTech IV Solution and Potential Impact

Based on PATH's substantial experience and knowledge about test development and introduction, HealthTech has set up the Rapid Diagnostic Tests web site, which provides summaries of relevant diagnostic information and links to available online resources. The web site strives to promote the appropriate use of rapid diagnostic tests. Staff developed the site to bring together information on available rapid test technologies for hepatitis B, HIV, malaria, and syphilis, and provide references to peer-reviewed literature detailing the accuracy of these tests and their appropriate use. A comprehensive table for each disease includes manufacturer contact information for available rapid diagnostic tests for four main diseases. Potential impact of this web site includes the ability of planners, managers, and laboratory staff to make better diagnostic test choices and improve program design both for individual diagnosis and disease surveillance.

Ultimate Goals and Objectives of HealthTech Project

- Provide current and relevant information to support proper use of rapid diagnostic tests.
- Improve contact between manufacturers and users of rapid diagnostic tests.
- Make rapid diagnostic test information easily available to policymakers with limited internet access.

Status of Project as of September 2004

The rapid-diagnostics.org web site continues to receive visits from users in many countries, and from academic, government, and private domains. Inquiries are made from program managers on the availability of different products. Topics most frequently investigated on the web site include HIV and hepatitis B diagnostics, test accuracy, and specific technology descriptions. A significant overhaul will be implemented in November 2004, with a launch announcement distributed to staff, manufacturers, professional organizations, and relevant web sites.

Milestones expected in the past six months	Achievements and progress towards milestones
Updated information and new links with additional text will be added to reinforce the objective of the site.	Links updated June 2004. Reworking of text and manufacturer's contact information postponed until November 2004.
Reworking of the statistics sections to be supported with some examples of field application of rapid diagnostic tests.	Completed June 2004.
Additional data on rapid diagnostic tests for hepatitis C to be added.	Not within scope of current funding.
News release about the updated web site combined with the addition of a feedback opportunity on the web site for users.	To be completed November 2004.

Problems encountered	Actions taken or plans to resolve
Expectation that web site represents manufacturing capacity.	November update will emphasize to users that the web site is not linked to a manufacturer or specific products.
Frequent changes in manufacturers' product lists and frequent differences between what is listed and what is available.	November update will include changes in manufacturers' products, and when possible, availability of product listed on web site will be verified. Links can continue to be monitored; however, without continued funding, November 2004 is the last update.
Overscheduled PATH webmaster.	Web master availability in November is verified.

Milestones expected in the next six months	Planned activities to reach those milestones
In November 2004 the final update will be posted.	Content review to be completed, new manufacturers identified, and product availability of existing manufacturers verified.
Inquiries to potentially interested organizations will attempt to secure funding for continued updates and potential expansion of web site.	Discussions with potentially interested organizations will be conducted. Relevance of web site service requires routine updates and makes continued funding important.

Other Technologies

Development of Single-Dose Packaging of Nevirapine Oral Suspension

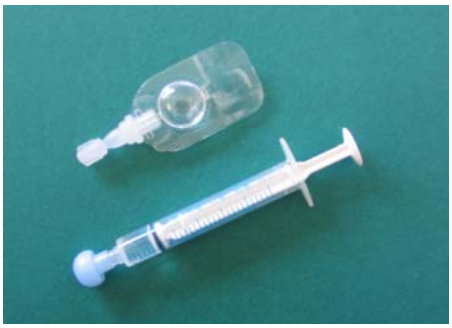
Health Need Addressed

Clinical trials have shown nevirapine (NVP) to be an efficacious therapy for reducing mother to child transmission (MTCT) of HIV.[1,2] Study results demonstrated that NVP is both low cost and practical. However, administration of NVP in resource-limited settings can be problematic given the requirement to deliver infant doses within 72 hours of birth, the high prevalence of home births, and the reluctance of health workers to open multi-dose bottles for single use due to wastage concerns. This is especially challenging in areas where there is limited use and limited availability of health care services. One important barrier to expansion of use is the absence of single-dose packaging for the pediatric oral suspension of NVP. As has been documented in immunization programs, health workers may be reluctant to open a 20 ml bottle of NVP (approximately 30 pediatric doses) to administer a single dose to an infant out of concern that the remaining doses will not be used before the expiration period of six weeks described on the label.[3] Single-dose packaging will be necessary in rural settings characterized by limited clinical capacity and/or low client load. It will also be essential for use in home births.

HealthTech IV Solution and Potential Impact

PATH is participating in a public-/private-sector collaboration with USAID, Population Services International (PSI), Boehringer Ingelheim (BI) (the manufacturer of nevirapine), and other partners to develop and introduce a single-dose package capable of delivering a pediatric dose of NVP oral suspension.

Now with HealthTech funding, PATH is conducting a detailed feasibility and implementation analysis of packaging options, new presentation development plans, and manufacturing scenarios that could create a sustainable supply of NVP in single-dose packages.



Uniject™[4] DP delivery device and Exacta-Med®[5] dispenser

[1] Guay LA, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet*. 1999; 354(9181):795-802.

[2] Moodley D, Moodley J, Coovadia H, et al. A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. *Journal of Infectious Diseases*. 2003; 187(5):725-35.

[3] Drain PK, Nelson CM, Lloyd JS. Single-dose versus multi-dose vaccine vials for immunization programmes in developing countries. *Bulletin of the World Health Organization*. 2003; 81(10):726-31.

[4] Uniject is a trademark of BD.

[5] Exacta-Med® is a registered trademark of Baxa Corporation.

Ultimate Goals and Objectives of HealthTech Project

The goal is to increase ease of use, availability, and ultimately the uptake of the infant oral dose of NVP for prevention of mother-to-child transmission (PMTCT). In order to achieve this goal, PATH will:

- Develop a detailed feasibility and implementation analysis of single-dose packaging options, new presentation development plans, manufacturing scenarios that could create a sustainable supply of NVP in single- or small-dose packaging, and the development of an implementation plan for the large-scale programmatic delivery of this PMTCT product and associated services.
- Identify, evaluate, and work with partners to introduce single-dose packaging capable of delivering the pediatric dose of NVP oral suspension.

Status of Project as of September 2004

Milestones expected in the past six months	Achievements and progress towards milestones
Demonstrate stability of NVP oral suspension in Uniject DP and Exacta-Med, single-dose packaging.	Initial results suggest NVP in Uniject DP is stable for 4 months at varying temperatures (August 2004). Exacta-Med is stable for 2 months and PATH is working to optimize packaging in order to extend stability.
Review protocols and provide technical assistance to PSI on the field acceptability study, planned for November 2004.	PATH's Institutional Review Board has approved a modification to the protocol for a study in Tanzania under minimal risk review (August 2004). The study will now evaluate use of both the Uniject DP and the Exacta-Med dispenser.
Demonstrate feasibility of small-scale filling approach for Exacta-Med dispenser.	Feasibility study confirmed volume accuracy and repeatability of small-scale Exacta-Med dispenser machine filling (May 2004).
Identification of secondary (outer layer) packaging options to improve stability and feasibility of field distribution of NVP-filled Baxa oral dosing syringes.	Foil pouch identified as packaging that would improve the stability, durability, and acceptability of distributing NVP prefilled Baxa oral dosing syringes in PTMCT programs (July 2004).
Determination of next steps for NVP in Uniject DP based on stability study results.	U.S. Pharmacopoeia (USP) confirmed that antimicrobial effectiveness testing as an alternative to parabens measurement would be acceptable. Consensus that project should move forward achieved at collaborator meeting (see below).

Increase visibility of the project in the global AIDS community.	Project leader attended International AIDS Congress (IAC) in Bangkok (July 2004). More than 300 project update sheets were distributed. Multiple contacts made with potential collaborators in the field.
Involve broader group of stakeholders in project.	Broad consensus achieved among stakeholders (PSI, USAID, Rational Pharmaceutical Management Plus, USP, PHR, and PATH), agreeing that project should move forward aggressively into the next phase (August 2004).
Continue to catalyze technical collaboration between BI, PATH, PSI, and USAID.	Project partners worked effectively to move the project forward into the next phase (ongoing).

Problems encountered	**Actions taken or plans to resolve**
Tanzania and Zambia acceptability studies not carried out as soon as originally planned due to protocol changes, in-country review requirements, and stakeholder consensus building.	Provided additional information and support to PSI to address in-country requirements. Tanzania has now been approved and will start in November. Zambia protocol is now moving through in-country approval processes. Anticipate Zambia study will start in December 2004 or January 2005.
Late breaker abstract not accepted for International AIDS Conference XV.	Project leader attended IAC 2004. Developed project update sheet and more than 300 project updates were distributed.

Milestones expected in the next six months	Planned activities to reach those milestones
Ongoing stability studies of NVP in Uniject DP at BI.	Monitor studies and participate in possible technical problem-solving discussions. Communicate updates to team and determine end point of stability study with remaining samples (9 months or 12 months).
Effectiveness of foil pouch to increase stability of Exacta-Med dispenser demonstrated.	Conduct evaporation study at PATH to document effectiveness of foil pouch in reducing moisture loss (determined by BI as key factor in loss of stability of dispenser after 2 months).
Stability studies of NVP in pouched Exacta-Med dispenser, either at BI or contract laboratory.	Negotiate one of two options with BI; conduct stability studies of NVP in pouched Exacta-Med dispenser or transfer of analytical method to contract lab to conduct study. Provide samples to determined lab.
Plans for technology transfer and production procedures.	For NVP in Uniject DP and Exacta-Med, develop full technology transfer and standard operating procedures documentation to support installation of small-scale filling and packaging systems in a targeted African country, likely to be either Zambia or Tanzania. Outcome of stability studies will impact the pace of this work.
Demonstration of acceptability of Uniject DP device and Exacta-Med dispenser.	Continue to support implementation of PSI-led acceptability studies in Tanzania and Zambia.
Establishment of working relationship with Axios in Tanzania.	Further build working relationship with Axios's Tanzania program and develop detailed work plan for pilot field study.

Microbicides Applicator Evaluation

Health Need Addressed

AIDS is the leading cause of mortality among adults aged 15 to 59 years.[1] Women are increasingly bearing the disproportionate burden of the AIDS epidemic. In 2003, women accounted for nearly fifty percent of all people living with HIV, compared to forty-one percent in 1997.[2] In Africa, women are 1.3 times more likely than men to be infected with HIV; young women aged 15-24 are 2.5 times more likely to be infected than young men.[3]

Due to social norms, gender inequalities, and economic disparities, women are often unable to protect themselves from HIV through abstinence, mutual monogamy, or male condom use. Safe, effective microbicides could provide urgently needed options for women and men seeking protection from HIV and other sexually transmitted infections.

With over 60 potential microbicides in preclinical or clinical trials, most research has focused on the gels/creams intended for topical application, with much less targeted research on the devices (applicators) that will be used to deliver the microbicides. The applicator devices will be critical in ensuring a safe, effective microbicide product. The applicator impacts the overall product's safety (relationship with product purity and stability, avoidance of local trauma associated with insertion or use), efficacy (consistent delivery of the required amount of product in the intended location) and acceptability (comfort, ease of use, disposability). Acceptability of the applicator, in addition to the microbicide, will greatly impact whether the product is used consistently and correctly. From past female condom research,[4] it is clear that user acceptability, in addition to product cost, is a major determinant of product uptake and actual use. Finally, the design of a product for worldwide users estimated at 34 to 88 million women per year[5] has a potential environmental impact in terms of waste disposal.

HealthTech IV Solution and Potential Impact

Modeling efforts have shown that a partially effective microbicide could avert over 2.3 million cases of HIV in three years, given certain levels of uptake, coverage, and use.[6] As noted above, the applicator will play a critical role in product uptake and use. We have the opportunity to evaluate and address these important issues before microbicide product introduction, so that appropriate applicators can be as accessible and acceptable as possible, leading to much greater levels of use-effectiveness and greater rates of HIV protection.

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[1] WHO. Facts and Figures from The World Health Report 2003–Shaping the Future. *WHO* 2003
[2] UNAIDS. Report on the Global AIDS Epidemic. UNAIDS. 2004
[3] UNFPA. State of the World Population. UNFPA. 2004
[4] Hoffman S, et al. The Future of the Female Condom. *Perspectives on Sexual and Reproductive Health* 2004.36(3):120-126.
[5] Pharmaco-Economics Working Group of the Microbicide Initiative. The Economics of Microbicide Development: A Case for Investment.
[6] Public Health Working Group of the Microbicide Initiative. The Public Health benefits of Microbicides in Low Resource Settings: Model Projections.

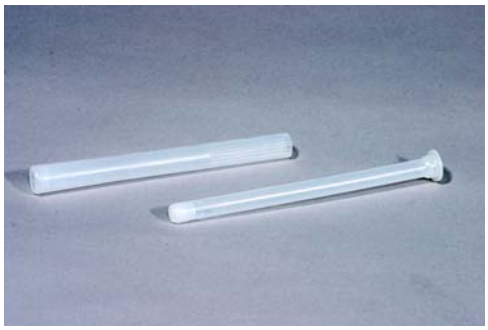
Ultimate Goals and Objectives of HealthTech Project

The goal of the project is to ensure that safe, appropriate, affordable applicators are available for use in low-resource settings at the time of microbicide introduction. The objectives of this project are to:

- Provide data that can inform product selection of devices for use in low-resource settings.
- Provide data on status and availability of existing applicators that meet cost, user, product, and manufacturing requirements.
- Strengthen linkages between applicator and microbicide researchers, developers, and sponsors to ensure timely and effective product introduction.

Status of Project as of September 2004

"Improving Topical Microbicide Applicators for Use in Resource-Poor Settings" authored by HealthTech staff was published in the July 2004 issue of the *American Journal of Public Health*. (Attachment 1) As of September 2004, we are initiating Stage III activities, including a search for an applicator manufacturer in two developing-country settings, and organizing a microbicide meeting to discuss regulatory needs and research priorities for bridging current microbicide products with lower cost, alternative applicators for product introduction. This meeting is being planned for July 2005. We are also completing the preparation of two articles for peer-review journals to report on results from the Applicator Safety Study and Acceptability Study using conjoint analysis. An article entitled "Delivering Microbicides: Considering Key Factors in Applicator Design" was published in *The Microbicide Quarterly* July/August/September 2004 issue. (Attachment 3)



Microbicide applicator

Milestones expected in the past six months	Achievements and progress towards milestones
Analysis of all three studies to be completed. 1) Clinical Safety Study 2) Acceptability Study 3) Material/Design Feasibility Analysis	Analysis of Clinical Safety Study and Material/Design Feasibility Analysis is complete. A manuscript has been prepared for the Clinical Safety Study for submission to peer-review journals. For the Acceptability Study, we have completed the full analysis of the South Africa data set and are currently finalizing the analysis of the Dominican Republic data set. A manuscript is also being prepared for sharing results of this study.

Identification of existing applicator manufacturers in developing countries whose products would be appropriate for use with microbicides per manufacturing, product, cost, and user criteria.	We were not initially funded for this activity; however we received approval from USAID in July to allocate some of our obligation towards this objective. We are now initiating a limited product search in South Africa and India to identify manufacturers who meet manufacturing, product, cost and user criteria.
Identification of appropriate participants for applicator/microbicide meeting.	In progress; applicator manufacturers will be determined based on outcomes of international scan and through discussions with U.S. manufacturers. Microbicide trial managers, sponsors, and developers will be identified based on status of microbicide (phase of clinical trial) and interest in adopting new applicators for product introduction. We will also be asking a group of policy, regulatory, and research stakeholders to review the criteria for the applicator manufacturer search, and this group will serve as the core group for this meeting.

Problems encountered	**Actions taken or plans to resolve**
Trouble scheduling appropriate staff to assist with analysis of acceptability study data.	We have scheduled an appropriate researcher within PATH to assist with data analysis.

Milestones expected in the next six months	**Planned activities to reach those milestones**
Finalize manuscripts for both Clinical Safety Study and Acceptability Study for publication in peer-reviewed journals.	For the Clinical Safety Study, PATH will prepare the manuscript per journal requirements. Profamilia collaborators in the Dominican Republic will take the lead in journal-submission process. For the Acceptability Study, we will complete analysis of Dominican Republic data and write manuscript. Collaborators in Dominican Republic and South Africa will review and provide input.

Conduct international search for applicators.	Develop business, design, and technical specifications for identifying appropriate applicator manufacturers. Have specifications reviewed by experts from FDA, CONRAD, USAID, International Program on Microbicides, and other appropriate regulatory and microbicide bodies. In India, work through PATH's India office to conduct scan of manufacturers, per manufacturer specifications. In South Africa, establish appropriate collaboration to conduct scan of manufacturers. South African collaborators will conduct scan, per manufacturer specifications. Continue contact with current U.S.-based applicator manufacturers to stay updated on product modifications (HTI, Tek-Pak).
Organize microbicide meeting to discuss regulatory needs and research priorities for bridging current microbicide products with lower cost, alternative applicators for product introduction.	Determine appropriate microbicide trial managers, developers, and sponsors, as well as regulatory experts and applicator researchers to participate in a microbicide policy meeting. Plan meeting logistics; meeting to be held at PATH's Washington, D.C. office.

Vasectomy Technologies

Health Need Addressed

Recently published evidence suggests that the rate of vasectomy failure (measured by unintended pregnancy) is around 4%,[1,2] with methods commonly used globally. Incorporation of improved methods, such as fascial interposition and thermal cautery, could help lower the rate of failure and increase acceptance of vasectomy.

HealthTech IV Solution and Potential Impact

FHI and EngenderHealth have recently published evidence confirming the clinical advantages of fascial interposition[3] and indicating possible advantages of thermal cautery.[4] To complement this research, PATH was asked to evaluate the physical durability and the potential for reuse of a thermal cautery device along with potential redesign or cost-reduction opportunities. The long-term goal of this collaboration is to permit introduction of a cautery vasectomy technique, in conjunction with recommended procedural and reuse methods, for introduction into low-resource settings.

Ultimate Goals and Objectives of HealthTech Project

- Verify that a cautery device (designated by the manufacturer as single use) is safe and effective for multiple uses.
- Provide technical assistance to other project partners for review of new devices, sourcing of generic devices, and sperm analysis.
- Conduct a cost-effectiveness evaluation for different currently used vasectomy methods.

Status of Project as of September 2004

- PATH is finalizing results from a second reuse evaluation (cleaning and disinfection).
- PATH is conducting a cost-effectiveness evaluation for vasectomy methods in multiple low-resource clinics.

[1] Wang D. Contraceptive failure in China, *Contraception*. 2002;66:173-178.
[2] Nazerali H, Thapa S, Hays M. Vasectomy effectiveness in Nepal: a retrospective study, *Contraception*. 2003; 67:397-401.
[3] Sokal D, Irsula B, Hays M. Vasectomy by ligation and excision, with or without fascial interposition: a randomized controlled trial, *BMC Medicine.* 2004;2:6.
[4] Barone M, Chen-Mok M, Sokal D, *BMC Urology.* 2004;4(1):10.

Milestones expected in the past six months	Achievements and progress towards milestones
PATH will complete reuse evaluation of vasectomy cautery tips.	Protocol was developed by PATH and reviewed by FHI. Final data is currently being received from contract laboratory.
Act as advisor to novel vasectomy technique developer.	PATH staff met with developer twice and recommended that the developer: • Begin to collect animal and human data in order to support claims. • Pursue introduction into U.S. standard practice before aggressively pursuing introduction into low-resource clinics.
Develop scope of work for cost-effectiveness analysis.	Scope of work was developed and discussed with both EngenderHealth and FHI. Initial cost model was developed and is in review at FHI. Initial literature review of effectiveness data was generated and reviewed by FHI.

Problems encountered	Actions taken or plans to resolve
Turn around of protocol development and studies by the contract laboratory was slower than initially predicted.	Because this information is not time-sensitive, no direct action was taken.

Milestones expected in the next six months	Planned activities to reach those milestones
Completion of cleaning and disinfection follow-up study.	After receipt and review of final data, reuse guidelines will be drafted for use during field introduction of cautery devices.
Complete clinic visits for cost-effectiveness analysis.	Work with EngenderHealth to determine clinical sites that represent different clinical conditions in Asia, Africa, and Latin America. Validate basic cost model in Latin America with clinical visits by PATH Seattle staff. Clinical visits in Asia and Africa by PATH field staff.
Compile and begin analysis of data from clinical visits.	Synthesize data and clinical differences to develop an overall cost model. Identify differences between high and low patient throughput clinics.

Basic Delivery Kit

Health Need Addressed

High rates of maternal and perinatal mortality in developing countries indicate a crucial need for new and innovative interventions for pregnancy and neonatal care. Most women have no access to maternity services due to distance, cost, and local customs; many give birth alone. High rates of neonatal and maternal tetanus and sepsis indicate a need for education and materials focused on clean birth practices.

HealthTech IV Solution and Potential Impact

The basic delivery kit is an inexpensive, simple kit designed to help create a clean birthing environment, particularly for home births. Based on a needs assessment in rural community settings, the contents selected for inclusion in the kit sold in Nepal include a clean razor blade, clean cord ties, a small bar of soap, a cord-cutting surface, pictorial instructions, and a polyethylene delivery sheet. The delivery kit is designed for use by trained and untrained traditional birth attendants, family members, and women who give birth unassisted in the home. The potential impact of the development and promotion of kits in local communities in Africa is great. To demonstrate the health effects of kit use, PATH has completed the first randomized community-based trial of single-use delivery kits in Africa. PATH is currently exploring partnership opportunities with a group in Ethiopia and is seeking funding for a local kit production project in that country.

Ultimate Goals and Objectives of HealthTech Project

The purpose of the study entitled “Evaluation of the effectiveness of a clean delivery kit intervention in preventing cord infection and puerperal sepsis among neonates and their mothers in rural Mwanza Region, Tanzania” was to determine the impact of a delivery kit intervention on reducing cord infection and puerperal sepsis among newborns and their mothers in rural Tanzania.

Status of Project as of September 2004

The study, done in collaboration with National Institute of Medical Research in Mwanza, Tanzania, was ended in May 2004. A total of 3,262 women were enrolled in the study, and final data analysis reflects lower rates of sepsis and cord infection among kit users and their infants. More detailed results follow:

- After adjusting for whether a mother had a bath before delivery, where the delivery took place and whether some substances were put on the cord stump, an infant whose mother used the delivery kit was about 13 times less likely to develop cord infection than an infant whose mother did not use the delivery kit. A newborn of a woman who bathed before delivery was also about 3 times less likely to develop cord infection than a newborn of a woman who did not bathe before delivery.
- After adjusting for whether a woman had a bath before delivery, where delivery took place, and duration of labor, a woman who used the kit for delivery was about 3 times less likely to develop puerperal sepsis than a woman who did not use the delivery kit. A woman who bathed before delivery was also about 3 times less likely to develop puerperal sepsis than a woman who did not bathe.
- Qualitative research activities were concluded in early 2003 and reported in previous semiannual HealthTech reports.

Milestones expected in the past six months	Achievements and progress towards milestones
Complete Tanzania delivery kit evaluation study.	Study completed.

Problems encountered	Actions taken or plans to resolve
N/A	

Milestones expected in the next six months	Planned activities to reach those milestones
Submit final report on Tanzania delivery kit study.	Final study report will be submitted to USAID by November 1, 2004.
Prepare and submit article on Tanzania delivery kit study to peer-review journal.	Article has been drafted and is scheduled for submission at end of November 2004.

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Attachment 1

Improving Topical Microbicide Applicators for Use in Resource-Poor Settings

With more than 60 potential microbicides being assessed in preclinical or clinical trials, most attention has been centered on products intended for topical application, with much less research conducted on the applicators that will be used to deliver the microbicides. However, applicator design relates to safety, efficacy, and acceptability.

As the foundation for a more systematic approach to evaluating and possibly improving designs for topical microbicide applicators, we conducted a literature review and a series of interviews with microbicide developers, trial investigators, and trial sponsors. Our findings indicate that issues concerning applicator safety, reuse, and cost warrant further investigation. (*Am J Public Health.* 2004;94:1089–1092)

Janet G. Vail, MPH, MBA, Jessica A. Cohen, MHS, and Kimberly L. Kelly, MPA

IN THE MIDST OF THE growing AIDS pandemic, safe and effective microbicides could provide urgently needed options for women and men seeking protection from HIV and other sexually transmitted infections. At present, more than 60 potential microbicides are being tested in preclinical or clinical trials. Most attention has been focused on the products themselves, with much less research addressing the devices (applicators) that will be used to deliver most of the microbicides now in the advanced clinical development stage. Applicator design relates to safety (e.g., relationship with product purity and stability, avoidance of local trauma associated with insertion or use), efficacy (e.g., consistent delivery of the required amount of product in the intended location), and acceptability (comfort, ease of use, convenience, aesthetic appeal).

According to interviews and literature reviews conducted by the Program for Appropriate Technology in Health (PATH), approximately 6 different applicators are in use in current microbicide trials. Most of these applicators, prefilled with a single dose to reduce dose variability among trial participants, have been adapted from applicators already marketed for other products. The Global Microbicide Project, directed by The Contraceptive Research and Development Program (CONRAD), a sponsor of several microbicide clinical trials, recently conducted physical tests on applicators and polled physicians and consumers regarding the appearance of these products. This work resulted in a prefilled applicator produced by HTI Plastics (Lincoln, Neb) that has been or will be used in evaluations of 8 different microbicides.

The Population Council has used the prefilled Micralax applicator, designed to deliver rectal laxatives, in its trials of the microbicide Carraguard. The Population Council conducted a 2-month study involving 22 women to evaluate the feasibility and acceptability of that applicator as a microbicide/placebo delivery system.[1] Finally, one microbicide developer based at Laval University in Canada has patented an applicator specifically for use with his product.

METHODS

We conducted a literature review as the foundation for a more systematic approach to evaluating existing applicators and assessing the need for improved applicator designs. The literature covered vaginal and rectal applicators, along with inserters for microbicides, spermi-

TABLE 1—Studies Addressing Vaginal and Rectal Product Applicator Acceptability, Dosage Delivery, Ease of Use, Reuse, or Size

Study, Setting, and Participants	Study Intervention	Product
Barnhart et al.[8]: US university medical center; 1 woman	Magnetic resonance imaging; 7 pelvic scans	Gynol-II mixed with a 1:100 concentration of gadolinium-based magnetic resonance contrast material, with "standard clinical applicator" (not specified)
Barnhart et al.[9]: US university medical center; 1 woman	Magnetic resonance imaging; 1 pelvic scan	Gynol-II mixed with a 1:100 concentration of gadolinium-based magnetic resonance contrast material, with "standard clinical applicator" (not specified)
Bentley et al.[2]: 2 hospitals in Rhode Island; 27 low-risk women aged 18–45 years	Product use once daily for 14 days and twice daily for 14 days (patient choice)	BufferGel with reusable applicator
Coetzee et al.[1]: 2 primary health care centers in South Africa; 28 women 18 years or older who were HIV negative	Product use every other day and up to 1 hour prior to vaginal intercourse over 2 months	Micralax applicator prefilled with methyl cellulose gel
Coggins et al.[6]: 5 sites (Cote d'Ivoire, Thailand [2 sites], United States, Zimbabwe); 145 women	Product use of each type for 4 weeks with each act of vaginal intercourse	Apothecus Vaginal Contraceptive Film; Ortho Conceptrol Vaginal Inserts (suppository); Ortho Conceptrol Gel in a prefilled applicator
Gross et al.[7]: Washington State; 35 seroconcordant male couples (25 HIV-negative and 10 HIV-positive)	Product use once or twice daily and with anal sex at least 3 times a week	Advantage 24 in a prefilled single-use applicator
Hammett et al.[3]: 3 sites (Connecticut, Rhode Island, Puerto Rico); 84 drug-involved women aged 25–44 years	Use of each product during sexual intercourse at least twice during a 3-week period	Lubrin Inserts (suppository); Replens Vaginal Moisturizer in a prefilled disposable applicator; Moist Again with a reusable applicator
Hardy et al.[4]: Brazil; 635 women aged 15–45 years	Individual interviews using a structured, precoded questionnaire; no product use	Clotrimazole plastic applicator; KY Plus applicator; clotrimazole aluminum applicator; Advantage 24 prefilled single-dose applicator; single-use envelope prepared by researchers
LePage et al.[5]: United States (not specified); 20 healthy women with vulvovaginal candidiasis	1 product use per evening for 3 consecutive nights	Femstat (2% butoconazole cream) in a prefilled applicator
Morrow et al.[10]: 4 sites (United States [2 sites], South Africa [2 sites]); 50 HIV-negative and 13 HIV-positive women aged 18–45 years	Product use once or twice daily for 14 consecutive days	Pro 2000 gel in single-dose tubes with individually wrapped single-use plastic applicators

cides, contraceptive devices, and therapies. Ten published articles provided information specific to applicator acceptability,[1–7] dosage delivery,[1,7–9] ease of use,[1–3,5–7,10] reuse versus single use,[3–5,7,10] or size[4,5,7] (see Table 1 for more information about the applicators and products included in each study, along with sample sizes, research settings, and study interventions). This information was used as the basis for a subsequent series of interviews with lead investigators of microbicide clinical, preclinical, and acceptability trials.

The 17 interviewees were identified from the Alliance for Microbicide Development's "microbicides product database," as well as by referrals made during interviews with potential respondents and referrals from the Global Campaign for Microbicides. They included clinical and behavioral scientists, microbicide developers and funders, trial designers, and sponsors representing approximately 30 trials and 7 applicator designs. Respondents provided information regarding applicator type and selection criteria; ease of use, comfort, features, cost, dosage delivery, and reuse; suggested improvements; and alternative delivery mechanisms (tablets, film, vaginal ring, cervical cup).

A number of researchers participated in more than one clinical trial, preclinical trial, or both and were able to discuss several trials and corresponding applicators during a single interview. Four researchers discussed information obtained from trials conducted in developing countries. This series of interviews highlighted the importance of more systematic field research on applicators to guide possible design and manufacturing improvements that will address the needs of future microbicide users in resource-poor settings.

RESULTS AND DISCUSSION

Our findings indicate that issues surrounding applicator safety, reuse, and cost warrant further investigation. These areas were identified on the basis of their importance in terms of acceptability and accessibility among developing-country populations and the fact that they had not been thoroughly investigated in previous research. In particular, safety, reuse, and cost issues need to be examined in relation to one another and how together they affect preferences of women in developing countries.

Safety

Given the potential for frequent and sustained use of microbicides and their intended use as a disease prevention method, applicator safety is a

paramount consideration in product design. Some researchers noted that the size and shape of applicators as well as methods for insertion may lead to cervical, vaginal, or rectal trauma and commented that additional research should be conducted to provide a more complete understanding of applicator use and its effect on user safety.

Researchers noted that women participating in trials in developing countries expressed concerns about the risks that might occur from washing and storing reusable applicators in unsanitary conditions. These concerns included recontracting sexually transmitted infections, HIV infections, or both; contracting diseases such as cholera; and transmitting sexually transmitted infections, HIV, or both to partners and other family members. In one study, HIV-positive women in the United States reported their belief that cleaning an applicator would be unsanitary and would cause infection.[10] Although the literature has not shown any evidence of infections being transmitted via reusable applicators, perceptions of such risks need to be addressed.

The US Food and Drug Administration categorizes vaginal applicators as class I medical devices, meaning that they present minimal potential for harm to the user and are simpler in design than other medical devices. Examples of other class I devices include elastic bandages, examination gloves, and hand-held surgical instruments. Vaginal applicators are exempt from premarket notification, as are most class I devices. Therefore, new stand-alone vaginal applicators can be marketed in the United States without prior Food and Drug Administration clearance.

Reuse

Our literature review indicated that, when asked, US users reported a preference for prefilled disposable applicators.[3,5,7] In a survey of Brazilian women, most preferred the concept of a single-use device.[4] In a study of women from the United States and South Africa, 44% of the respondents preferred the idea of a single-use applicator as well.[10] In interviews, respondents reported that they favored using prefilled single-use applicators in clinical trials to simplify user participation requirements (eliminating the need for women to fill and clean the applicator themselves) and to reduce potential dose variability and user compliance errors associated with reusable applicators.

Outside of clinical research, decisions about reusable versus single-use applicators are intertwined with considerations of safety and cost, as well as convenience, portability, storage, undisclosed use, and disposal. According to 2 of the researchers interviewed, some women in developed countries have voiced concern over adding to environmental waste with disposable applicators, while others prefer single-use, disposable applicators as a result of their convenience. Conversely, 2 other researchers noted that women in developing countries were concerned about privacy of disposal and that they would prefer applicators that could be safely incinerated after use. This issue will have implications for determining the types of materials from which to make applicators.

According to a study conducted in the United States, women who have frequent sexual relations away from their homes found the characteristics of applicator storage and portability to be important.[3] Interviews with researchers suggested that women in developing countries may have greater concerns related to both discreet use and storage than women in industrialized countries, who may have more personal privacy. The inconvenience of having to wash an applicator in public places visible to neighbors or family members, as well as lack of accessible and clean water and fear of not being able to adequately clean the applicator, might lead women in developing countries to prefer single-use disposable applicators. Ultimately, both prefilled single-use and reusable applicators are likely to be needed to accommodate different user preferences and markets.

Cost

Cost will probably be one of the key determinants affecting access to microbicide products. Although one study has estimated single-use applicator prices[11] and 2 studies have explored what women in developing countries would be willing to pay for a microbicide,[12,13] the issue of cost as it relates to single-use versus reusable applicators has not been explored in developing-country populations. While users in some settings may prefer single-use products, the presumed higher cost of single-use applicators is an important decisionmaking factor in resource-poor settings. Nevertheless, alternative designs, less costly raw materials, and streamlined or simplified production processes could reduce manufacturing costs.

RECENT FIELD STUDIES AND ANALYSES

On the basis of the needs identified in this research, PATH, along with collaborating agencies, initiated 2 microbicide applicator field studies in September 2003, one to evaluate microbicide applicator safety and one to explore applicator acceptability. In the first study, PATH collaborated with Profamilia in the Dominican Republic to conduct a clinical evaluation of 3 microbicide applicators. The objective of this safety study was to assess and compare the applicators' effects on symptoms and signs of vaginal irritation as observed via colposcopy. The 3 applicators evaluated were a single-use applicator manufactured by HTI Plastics, a reusable applicator manufactured by HTI Plastics, and a single-use applicator (the Micralax applicator, manufactured by Norden-Pac International, Kalmar, Sweden). All applicators were empty and therefore not delivering any substance during use.

The second study was conducted in the Dominican Republic and South Africa in collaboration with Profamilia and the Reproductive Health Research Unit, respectively. The objective of this acceptability study was to characterize and prioritize women's needs as they relate to vaginal applicator features. The specific parameters explored were cost, reuse, and perceived applicator safety. In each country, approximately 450 interviews were conducted with randomly sampled participants from selected clinic populations. Actual applicator use was not part of the study.

Conjoint analysis, a quantitative method involving structured surveys and closed-ended inter-

views, was used to estimate preferences among potential microbicide users in the 2 populations sampled. Conjoint analysis is typically applied in economics and marketing fields; its application to health care interventions is more limited. However, a study applying conjoint analysis to HIV testing provides a good overview of the methodology and how it can be applied to the health field.[14] The methodology has also been applied to microbicide research and development.[15]

In conjunction with these 2 field-based studies, PATH conducted an analysis of different materials and applicator designs in an effort to characterize comparative features in the areas of cost, reuse, and disposal. This analysis assessed biodegradability of materials, effectiveness with which applicators could be cleaned, and alternative materials and fabrication techniques designed to decrease product cost.

Data collection is complete for all studies, and results are expected to be published later in 2004. If results of the safety study, acceptability study, and material/design analysis indicate a need for further refinement or adaptation of applicators for use in resource-poor settings, PATH will first assess existing products marketed by the private sector in both developed and developing countries, where numerous applicator products have been created for a variety of cosmetic and medicinal purposes (e.g., cardboard applicators manufactured for tampon use and medicine delivery). If these products require further research and development, PATH will work with its industry partners to adapt their products in an effort to ensure the availability of low-cost applicators that will meet user needs as well as microbicide delivery requirements. ■

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Contributors

J.G. Vail conceived the study, synthesized the findings, and revised the article. J.A. Cohen supervised all aspects of study implementation and led the analysis. K.L. Kelly implemented the study and assisted with the data analysis and the writing of the article.

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Attachment 2

MAJOR ARTICLE

Tuberculosis Serodiagnosis in a Predominantly HIV–Infected Population of Hospitalized Patients with Cough, Botswana, 2002

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A sensitive and accurate tuberculosis (TB) serodiagnostic test would aid in the control of TB, but results of current tests are relatively unreliable for persons infected with human immunodeficiency virus (HIV). We evaluated a new prototype immunochromatographic strip test and 5 commercially available serodiagnostic TB tests in a prospective study comprised of 465 consecutively enrolled patients with suspected TB from 2 hospitals in Botswana. Consenting adults underwent HIV testing, ⩾2 sputum smears and cultures, and mycobacterial blood culture. Patients were defined as having TB on the basis of any positive smear or culture. Between January and September 2002, 465 of 498 consecutive patients consented to enrollment. A total of 384 patients (83%) were infected with HIV, and 175 (38%) had TB; the mycobacterial blood culture was the sole source of diagnosis for 26 patients (15%) with TB. Among the tests evaluated, the sensitivity was 0%–63%, the specificity was 39%–99%, the positive predictive value was 0%–39%, and the negative predictive value was 63%–65%. We conclude that the serodiagnostic tests evaluated in this study lacked sufficient sensitivity as sole tests for TB in this population.

The current pandemic of HIV infection has contributed substantially to the recent increase in the worldwide incidence of tuberculosis (TB) [1]. TB is already the leading cause of death among people with AIDS, accounting for almost one-third of deaths among HIV-infected patients worldwide and ~40% of deaths among such patients in Africa alone [2]. In Botswana in 2001, the TB rate was 620 per 100,000 population [3], and the HIV prevalence among antenatal women was 35% [4]. Among hospitalized patients with suspected TB in 2001, 84% were infected with HIV [5].

Since 1996, the World Health Organization has promoted the strategy of "directly observed therapy, short course" for TB control, one aspect of which is case detection using sputum smear microscopy for patients with suspected TB in general health services [6]. The emphasis on TB diagnosis by sputum smear microscopy has limitations, primarily because the sensitivity—when direct, unconcentrated methods are used—is 40%–60% for a combination of 3 examinations [7, 8] and is lower for those with HIV coinfection [9]. Additionally, persons with HIV infection are more likely to have extrapulmonary manifestations of TB disease.

Serodiagnostic technology offers the potential for a rapid, inexpensive field-test for TB. The US Food and Drug Administration (FDA) has proposed 6 performance criteria for the ideal TB test (M. Goldberg, personal communication). A serological test should be accurate, with adequate performance to monitor response to therapy; able to discriminate between latent and active *Mycobacterium tuberculosis* infection, previous bacille Calmette-Guérin vaccination, or exposure to other potentially cross-reacting nontuberculous mycobacteria; rapid (duration, <25 min); capable of testing few

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or many patients; simple and safe for use by technicians without extensive training; stable at ambient temperature for up to 2 years; and affordable.

An immunochromatographic strip (ICS) test was developed by the Program for Appropriate Technology in Health (PATH; Seattle) with funds from the US Agency for International Development. The PATH prototype ICS test was used to retrospectively screen a panel of serum samples obtained from 284 HIV-negative adult patients in 4 African countries and Brazil, India, and Indonesia. Compared with culture, the mean sensitivity of the ICS test was 72% (range, 62%–100%). The specificity was 79% for ICS analysis of only 89 specimens from culture-negative subjects. ICS testing of specimens obtained from 92 HIV-infected subjects had a sensitivity of 41%; the specificity has not been quantified for HIV-infected subjects.

The chief goal of this study was to prospectively evaluate, under field conditions, the programmatic use and accuracy of ICS testing among inpatients with suspected TB. This study was also designed to assess the sensitivity and specificity of 5 other commercially available products or newly developed prototypes for TB serodiagnostic analysis.

PATIENTS, MATERIALS, AND METHODS

Patients. Patients aged ⩾18 years who had suspected TB and were hospitalized at either of the country's 2 referral hospitals were eligible for enrollment. Patients were defined as having suspected TB if they had a history of cough lasting ⩾2 weeks and were identified by their supervising physician as needing an evaluation for TB. They were prospectively identified by research staff who attended the hospital physicians' morning report.

Research staff explained the purpose and the conduct of the study and requested written informed consent in the patient's native language or in English. Approval for human subjects research was obtained from an institutional review board of the US Centers for Disease Control and Prevention, the PATH Human Subjects Protection Committee, the Health Research and Development Committee (Botswana), and the ethics review boards of the 2 participating hospitals.

Once enrolled, subjects underwent evaluations considered to be routine for suspected TB in Botswana: blood samples were obtained by phlebotomy for HIV testing and measurement of $CD4^+$ T lymphocyte count. Additionally, posteroanterior chest radiographs were obtained and read by the hospital staff radiologist, who was unaware of results of the serodiagnostic tests. Each patient was instructed to provide 2 sputum specimens produced at random times and 1 produced during the early morning for acid-fast bacillus (AFB) smearing and culture within 72 h of enrollment. A patient who could not produce sputum specimens underwent sputum induction, which was performed using 3% normal saline. In addition, blood was cultured for bacteria and mycobacteria. A tuberculin skin test (TST) using 2 tuberculin units of RT23 was performed, and induration was measured 48–72 h later. Other tests were performed at the discretion of the attending physician.

HIV testing. Serum HIV testing was performed according to the guidelines and procedures approved by the Botswana Ministry of Health at the time of the study. Serum samples were evaluated using 2 ELISA tests run in parallel (Murex HIV 1.2.0, Murex Biotech; and Ortho HIV1/HIV2 Capture ELISA System, Ortho Clinical Laboratories), each of which can detect HIV-1 and HIV-2. HIV infection was defined as 2 positive ELISA results. Non–HIV infection was defined as 2 negative ELISA results. Discordant results were resolved with Western blot testing.

Mycobacterial testing. AFB smears were analyzed using Ziehl-Neelsen staining. Sputum was cultured for mycobacteria on Lowenstein-Jensen slants using MGIT (Becton Dickinson), in accordance with the manufacturer's instructions. Blood was cultured for mycobacteria using MycoF Lytic (Becton Dickinson), in accordance with the manufacturer's instructions.

Serological testing. A total of 4 rapid tests (PATH ICS test, American Bionostica, Osborne Scientific, and MycoDot [Dynogen]) and 2 ELISAs (Omega Diagnostics and Anda Biologicals) were evaluated in this study. All laboratory personnel were trained in the use of rapid serological and ELISA-based tests before patient enrollment and testing. All non–ELISA-based testing was conducted on blood serum specimens, and PATH ICS testing was conducted on whole blood specimens on the days on which specimens were obtained. Serum specimens obtained for ELISA-based testing were frozen to −70°C on the day of collection and were tested when enrollment was completed. All tests were interpreted in accordance with manufacturers' or developers' instructions. The test reader was blinded to the patients' clinical status and the results of all other clinical tests. The rapid tests were read by 2 independent readers, and any discrepancy between the 2 readers was resolved by a third independent reader who was blinded to the findings of the 2 readers and the results of the clinical tests. For the ELISAs, indeterminate results were not included in performance calculations. For the Anda Biologicals ELISAs, an integrated positive result was calculated using any positive results of the IgG, IgM, and IgA ELISAs. Similarly, integrated negative and indeterminate test results were calculated using any negative or indeterminate results with the IgG, IgM, and IgA ELISAs.

Statistical analysis. Patients were defined as having TB disease on the basis of a positive AFB sputum smear or a sputum or blood culture that yielded *M. tuberculosis*. Statistical analysis was performed using Epi Info 6.04d for determination of the specificity and positive and negative predictive values of the serodiagnostic tests [10].

Because a gold standard for TB diagnosis does not exist, a

sensitivity analysis was also performed. Patients were grouped according to potential risk factors for TB, including HIV seropositivity, positive results of TST, abnormal chest radiograph findings, and reported history of exposure to TB or active TB disease. We then assumed that patients had active TB at the time of evaluation, regardless of whether it was detected by sputum smears or culture, blood culture, or some combination of these, and recalculated the sensitivity of the ICS test.

RESULTS

Patients. Of 498 consecutive eligible patients with suspected TB, 465 (93%) agreed to participate and were enrolled between January and September 2002. The median age was 36 years (range, 21–89 years); 53% were men. Characteristics by TB status are shown in table 1. Univariate analysis revealed that subjects with TB disease were less likely to report headache and a previous diagnosis of TB and were more likely to be younger and have night sweats than were subjects without TB.

Diagnostic evaluations. Table 2 summarizes the clinical characteristics of patients according to TB status. Overall, 384 patients (83%) were infected with HIV, 39 (8%) were HIV negative, and 42 (9%) declined testing or had missing results. Among 370 HIV-infected subjects for whom $CD4^+$ T lymphocyte counts were available, the mean T lymphocyte count was 81 cells/μL (median, 41 cells/μL); among 37 HIV-negative subjects, the mean $CD4^+$ T lymphocyte count was 495 cells/μL (median, 518 cells/μL). Among HIV-infected subjects, 324 (84%) had a $CD4^+$ T lymphocyte count <200 cells/μL.

A total of 382 subjects (82%) had an abnormal chest radiograph finding, of whom 369 (97%) had infiltrates, 52 (14%) had pleural effusions, 21 (5%) had cavities, 21 (5%) had a miliary pattern, and 1 (<1%) had a mass lesion. TB was diagnosed in 175 (38%) of 465 study subjects and was identified on the basis of sputum smears and/or culture only for 92 (53%), sputum examination (smear and/or culture) and blood culture for 57 (33%); and blood culture only for 26 (15%). Thus, mycobacterial blood culture yielded *M. tuberculosis* for 83 (18%) of 465 study subjects.

Among the 175 patients with TB, 72 (41%) had positive results of sputum smear and culture, 38 (22%) had positive smear results and negative culture results (12 had positive blood culture results—that is, results of sputum cultures were falsely negative), and 39 (22%) had negative smear results and positive culture results (8 had positive blood culture results—that is, sputum smears were negative for *M. tuberculosis*). The remainder of the patients with TB (26 [15%]) received diagnoses solely on the basis of positive blood culture results. Sputum induction was performed a total of 74 times for 39 subjects. Twelve patients were identified as having pulmonary TB solely on the basis of analysis of specimens obtained from sputum induction.

There were no statistically significant differences in mean TST sizes between patients with and patients without TB, regardless of whether TST readings of 0 mm were excluded from analysis (table 2). However, when readings of 0 mm were included, mean TST sizes were lower for those with HIV infection than for those without (1.8 vs. 5.6 mm; $P < .001$), but when such readings were excluded, mean TST sizes were not signif-

Table 1. Characteristics of 465 patients with suspected tuberculosis (TB), Botswana, 2002.

Characteristic	Subjects with TB (n = 175)	Subjects without TB (n = 290)	P[a]
Male sex	93 (53)	152 (52)	.92
Age, median years (range)	33 (21–89)	38 (21–84)	<.001[b]
Cough duration, median weeks (range)	9.2 (2–80)	8.6 (2–52)	.91
Productive cough	154/174 (89)	259/290 (90)	.81
Fever	140/173 (81)	238/290 (82)	.68
Weight loss	149/171 (87)	226/282 (80)	.08
Diarrhea	60/170 (35)	76/290 (26)	.09
Dyspnea	124/175 (71)	222/290 (77)	.26
Chest pain	144/173 (83)	250/287 (87)	.32
Night sweats	144/173 (83)	211/290 (73)	.02[b]
Headache	61/174 (35)	145/290 (50)	.002[b]
History of TB exposure	64/160 (40)	92/258 (36)	.50
History of TB diagnosis	28/175 (16)	80/275 (29)	.005[b]
History of tobacco use	68/175 (39)	124/290 (43)	.39
History of working in mines	17/175 (10)	48/290 (17)	.06
Died during hospitalization	21/168 (13)	53/285 (19)	.08

NOTE. Data are no. (%) of patients, unless otherwise indicated.

[a] By univariate analysis.

[b] Statistically significant.

Table 2. Results of evaluation of 465 patients with suspected tuberculosis (TB), Botswana, 2002.

Characteristic	Subjects with TB (n = 175)	Subjects without TB (n = 290)	P[a]
Abnormal chest radiograph findings	139/152 (91)	243/261 (93)	.51
TST reaction, mean diameter in mm (range)			
Overall	1.7 (0–105)	2.5 (0–115)	.19
Excluding patients with no response[b]	13.1 (2–105)	14.3 (2–115)	.16
HIV infection	150/175 (86)	234/290 (81)	.002
$CD4^+$ cell count, cells/μL[c]			
Mean	80	140	.23
<200	126 (87)	205 (78)	.04
Positive culture results			
Sputum[d]	19/38 (50)	48/91 (53)	.79
Blood[e]	9/175 (5)	26/288 (9)	.15
WBC count, ×1000 cells/dL	7.0 (0.3–25.2)	7.3 (0.5–27.9)	.83
Hemoglobin level, g/dL	8.7 (3.3–15.9)	9.9 (3.3–28.5)	.001
Hematocrit, median % (range)	26.1 (10.7–47.4)	29.5 (9.7–52.2)	.001
Platelet count, median cells ×1000 per mL (range)	242.3 (10–651)	284.8 (11–976)	.001

NOTE. Data are no. (%) of patients, unless otherwise indicated. TST, tuberculin skin test.

[a] By univariate analysis.
[b] Diameter, 0 mm (19 patients with TB and 40 patients without TB).
[c] Includes patients with and patients without HIV infection.
[d] Excluding mycobacteria; included 6 gram-negative rods, 5 *Candida* species, 3 pseudomonads, 3 gram-positive cocci, and assorted other pathogens.
[e] Excluding mycobacteria; included 9 *Staphylococcus aureus*, 9 other gram-positive cocci, and 4 gram-negative rods. The remaining 12 patients had isolates that were not otherwise specified by the central microbiology laboratory.

icantly different (14.9 vs. 11.9 mm; $P = .25$). Patients with HIV infection were more likely to be anergic after TST was performed than were those without HIV infection (269 [70%] vs. 17 [44%]; $P < .001$). Subjects with TB were more likely to be anergic than were subjects without TB, though the difference was not statistically significant (125 [71%] vs. 188 [65%]; $P = .3$). In univariate analysis, subjects with TB disease were significantly more likely to have HIV infection, a $CD4^+$ T-lymphocyte count <200 cells/μL, and lower hemoglobin levels, hematocrit, and platelet counts than were subjects without TB (table 2).

Results of serodiagnostic analysis. The sensitivity, specificity, and positive and negative predictive values of the serodiagnostic tests are shown in table 3. When used to analyze serum specimens, the ICS test showed an overall sensitivity and specificity of 25% and 75%, respectively. Results of the ICS test were less satisfactory when used to analyze whole blood. When considered on the basis of its 3 component antigens, no single antigen outperformed the integrated result. When stratified by HIV infection status, the ICS test (serum) showed higher sensitivity for HIV-negative patients, compared with HIV-positive patients (40% vs. 26%), but the specificity was lower (65% vs. 76%). When stratified by $CD4^+$ T lymphocyte count >200 cells/μL, the ICS test showed higher sensitivity for patients with higher $CD4^+$ T lymphocyte counts, compared with those with <200 cells/μL (32% vs. 26%), but lower specificity (61% vs. 79%). When stratified by diameter of the TST reaction, the ICS test showed higher sensitivity for a TST diameter >5 mm, compared with a diameter <5 mm (38% vs. 26%), but lower specificity (71% vs. 75%). When stratified by chest radiograph findings, the ICS test showed higher sensitivity for subjects with abnormal findings, compared with those with unremarkable findings (26% vs. 7%), but lower specificity (76% vs. 88%). Compared with the overall findings, there was no significant difference in the results of the ICS test for patients with sputum smears negative for AFB (sensitivity 25% and specificity 74%) or for patients with a negative mycobacterial blood cultures (sensitivity 29% and specificity 75%).

Results of the sensitivity analysis for the ICS are shown in table 4. We assumed that all patients had active TB, regardless of whether TB was detected by sputum smearing and/or culture and/or by blood culture. We then recalculated the sensitivity of the ICS test. Statistical analysis revealed that sensitivity does not significantly improve in scenarios with >100 high-risk TB suspects. When analyzed in combination, the PATH ICS and Osborne Scientific tests together were 56% sensitive but only 46% specific for TB disease. For the Anda IgG, IgM, and IgA tests, 28%, 18%, and 15% of results, respectively, were indeterminate; for Omega, 34% of results were indeterminate.

DISCUSSION

In this study, TB and advanced HIV infection were relatively common among hospitalized patients with a history of cough

Table 3. Statistical analysis of serodiagnostic tests for tuberculosis (TB) among 465 hospitalized patients with suspected TB, Botswana, 2002.

Test	Sensitivity	Specificity	PPV	NPV
ICS (PATH)				
Serum	27 (47/172)	75 (216/289)	39 (47/120)	63 (216/341)
Whole blood	11 (19/172)	90 (259/285)	39 (19/49)	63 (259/412)
Osborne Scientific	37 (57/154)	63 (174/275)	36 (57/158)	64 (174/271)
MycoDot (Dynagen)	3 (5/147)	99 (259/263)	56 (5/9)	65 (259/401)
American Bionostica	0 (0/156)	99 (273/276)	0 (0/3)	64 (273/429)
Anda Biologicals				
IgG[a]	56 (64/114)	45 (98/220)	34 (64/186)	66 (98/148)
IgM[a]	26 (36/139)	83 (204/246)	46 (36/78)	66 (204/307)
IgA[a]	34 (50/145)	71 (155/219)	44 (50/114)	62 (155/250)
Integrated[b]	63 (109/174)	39 (114/289)	38 (109/284)	64 (114/179)
Omega Diagnostics[c]	43 (53/122)	52 (117/224)	33 (53/160)	63 (117/186)

NOTE. Because of sample loss or operator error, not all specimens were evaluated with each serodiagnostic test. Therefore, given the variation among denominators, calculations are shown in parentheses. ICS, immunochromatographic strip; NPV, negative predictive value; PATH, Program for Appropriate Technology in Health; PPV, positive predictive value.

[a] A total of 28%, 18%, and 15% of the results for Anda IgG, IgM, and IgA, respectively, were indeterminate and were not included in performance calculations.

[b] Performance was calculated by considering any positive result of the IgG, IgM, and IgA tests as an integrated positive result; all negative results of the IgG, IgM, and IgA tests as an integrated negative result; and all indeterminate results as an integrated indeterminate result.

[c] A total of 34% of the results were indeterminate and were not included in performance calculations.

lasting ⩾2 weeks. We found that the mycobacterial blood culture was a useful adjunct for TB diagnosis: 15% of all TB cases were diagnosed solely on the basis of blood culture results. This finding is consistent with those of previous reports [11, 12].

The subjects in and the setting of our study comprise the clinical scenario in which a TB serodiagnostic test is most needed: patients with suspected TB in a hospital with a high prevalence of HIV infection. The serodiagnostic tests we eval-

Table 4. Sensitivity analysis for tuberculosis (TB) serodiagnostic tests among 465 hospitalized patients with suspected TB, Botswana, 2002

	TB risk factor[a]					
Patient group, by presence of risk factor	HIV infection	Positive TST result	Abnormal chest radiograph finding	TB exposure	History of TB	Revised ICS sensitivity[b]
A	Yes	…	…	…	…	24 (93/380)
B	…	Yes	…	…	…	28 (16/58)
C	…	…	Yes	…	…	25 (94/379)
D	…	…	…	Yes	…	26 (41/156)
E	…	…	…	…	Yes	25 (27/108)
F	Yes	Yes	…	…	…	22 (8/37)
G	Yes	Yes	Yes	…	…	19 (6/31)
H	Yes	Yes	Yes	…	Yes	20 (1/5)
I	Yes	Yes	Yes	Yes	Yes	50 (1/2)
J	…	Yes	Yes	Yes	Yes	33 (1/3)
K	…	…	Yes	Yes	Yes	35 (8/23)

NOTE. ICS, immunochromatographic strip; TST, tuberculin skin test.

[a] When the presence of a risk factor is not indicated, it is considered to be unknown (i.e., present or absent) and/or unreported (e.g., patients in group K had an abnormal chest radiograph finding, a history of TB exposure, and TB disease but a positive, negative, or unknown HIV infection status and TST result).

[b] Because of sample loss or operator error, not all specimens were evaluated with each serodiagnostic test. Therefore, given the variation among denominators, calculations are shown in parentheses.

uated had a poor ability to detect TB in this population. The literature is replete with apparently successful evaluations of various TB diagnostic tests [13–17]. However, unlike our study, often only patients with AFB sputum smear–positive pulmonary TB disease are included, and those with paucibacillary pulmonary (i.e., AFB sputum smear–negative) disease (which may elicit a less vigorous host antibody response [18]) and control subjects with diseases that mimic TB (e.g., endemic mycotic or nontuberculous mycobacterial disease or sarcoidosis) are not.

Because HIV infection has become such a prominent feature of the TB epidemic in many parts of the world, evaluations of new tests should examine the effects of HIV on serodiagnostic assay results. In initial studies performed in preparation for commercial release of the MycoDot assay, sensitivity was 63% among HIV-negative subjects with TB but was only 40% among HIV-infected subjects [19]. In another evaluation, this assay correctly identified only 9 (11%) of 85 patients with TB who were also infected with HIV [20]. In Tanzania, the sensitivity of the MycoDot assay was only 16%, and the specificity was 84% [21]. Among HIV-infected subjects with paucibacillary disease, sensitivity of this assay was only 3% [21]. Results of these studies are consistent with those of the current study.

In the laboratory-based development phase, the ICS test showed promising performance when used to analyze banked serum specimens. However, in the field-testing phase, it lacked sufficient sensitivity as the sole test for TB. There was a significant reduction in test sensitivity when whole blood was used as the clinical sample. This result indicates that additional assay optimization is required to facilitate the use of whole blood in future clinical evaluations of the test.

The ELISA-based tests used in this study (Omega and Anda) were associated with a high rate of indeterminate results, which suggests that the cutoff values for the assays were suboptimal for use in the population in this study. It is possible that, with successive testing (which was not done in this study), the proportion of indeterminate test results may decrease. However, among those specimens that yielded an interpretable result, performance was also relatively poor. In general, it is thought that there is decreased mycobacterial antibody production in patients coinfected with *M. tuberculosis* and HIV that challenges the limits of detection of most ELISAs [22, 23].

The most important limitation of this study is that *M. tuberculosis* culture is not a perfect gold standard for diagnosing TB, even when performed in conjunction with blood cultures. In addition, all eligible patients did not consent to participation, which may have resulted in an underestimation of the prevalence of HIV infection in this population, because lack of consent was most often the result of reluctance to undergo HIV testing. We did not test all available serodiagnostic assays and, therefore, cannot conclude that there is no test or combination of tests that could be useful in the development of a clinical algorithm for increasing the accuracy of diagnosing TB.

In conclusion, the serodiagnostic assays evaluated in this study are not sufficiently sensitive and specific for routine application in the diagnosis of TB in Botswana or similar regions where HIV infection is highly prevalent. Therefore, these assays fail the first performance criterion of the FDA for the ideal TB test (M. Goldberg, personal communication). Mycobacterial blood cultures should be considered as a viable adjunct to diagnosing TB in regions with a high volume of patients coinfected with HIV and TB and with the resources and technical capacity to permit their use.

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Attachment 3

DELIVERING MICROBICIDES: CONSIDERING KEY FACTORS IN APPLICATOR DESIGN

Jessica Cohen

To complement the growing body of research on microbicides, the Program for Appropriate Technology in Health/PATH is undertaking focused research on microbicide delivery mechanisms to ensure that safe, effective, and acceptable devices are available once a microbicide is ready for market. The design of such a mechanism relates directly to:

Product safety:

- It should not cause vaginal or cervical trauma with insertion or use,
- It should maintain product purity and stability,

Product effectiveness:

- It should provide consistent delivery of required amount of product in the intended location, and

Product acceptability:

- It should be comfortable, convenient, and easy to use, store, and dispose of.

While the majority of microbicide clinical trials are now using pre-filled, single-use, plastic applicators, other applicator designs and delivery mechanisms should be explored so that there is a range of affordable and appropriate methods for wide-scale introduction. Cervical barriers such as diaphragms and cervical caps should also be considered as additional microbicide delivery options for women seeking dual protection.

Baseline Applicator Research

Beginning in 2002, PATH conducted a systematic review of all applicators currently used in microbicide clinical trials, in order to characterize their benefits and limitations with regard to dosage delivery, acceptability, ease of use, cost, comfort, and safety.[1] This assessment included a literature review and interviews with clinical and behavioral scientists, microbicide developers, trial designers, and sponsors, representing 30 trials and 7 distinct delivery mechanisms. The results of this review indicated that the issues of applicator safety, re-use, and cost warrant further research, particularly for their relevance to the needs of women in developing countries, where these products are most needed and will first be introduced. Based on these findings, PATH and collaborating agencies conducted three additional applicator studies to evaluate these issues.

Applicator Safety

Some researchers interviewed for the baseline study expressed concern that applicator size, shape, and method of insertion could lead to cervical or vaginal trauma, an important safety issue, and that additional research was needed to assess such effects. While colposcopy and other methods are used to assess vaginal trauma and irritation during microbicide clinical trials, safety outcomes are focused on the microbicide product itself, and collection of specific data pertaining to the delivery mechanism is not standard. The US Food and Drug Administration classifies vaginal applicators as Class I medical devices, indicating that they present minimal harm to users and are therefore subject to minimal regulatory control. However, the potential for frequent and sustained use of microbicide products for disease prevention makes the safety of the applicator itself a critical component of overall product safety.[2]

PATH, in collaboration with Profamilia in the Dominican Republic, designed a pilot study to assess and compare the effect of three vaginal applicators on signs and symptoms of irritation of the external genitalia, vagina, and cervix as observed by colposcopy after a single applicator use. Conducted in a Profamilia clinic in Santo Domingo, this study evaluated three applicators: an HTI Plastics single-use applicator, an HTI Plastics reusable applicator, and a Norden Pac (Micralax®) single-use applicator. Twenty women participated in the study. Each participant evaluated a single applicator at each of three visits and each of the three visits were conducted 7 to 14 days apart; in total, 20 women evaluated all three applicators for a total of 60 applicator uses. Colposcopy was conducted before and after insertion and removal of each applicator. The applicators were provided empty (without any placebo or microbicide gel) and without their plungers (two of the three had plungers) to reduce confounding of colposcopy results.

[1] Vail J, Cohen J, Kelly K. Improving topical microbicide applicators for use in resource-poor settings. American Journal of Public Health 94(7):1089-92. July 2004.

[2] US Food and Drug Administration. 21 CFR 884.4530 (2003). Obstetric-Gynecologic Specialized Manual Instrument.

DELIVERING MICROBICIDES *(Continued from p.15)*

TABLE 1. COLPOSCOPIC FINDINGS AFTER APPLICATOR USE

FINDING	HTI SINGLE-USE N=20	HTI REUSABLE N=20	NORDEN PAC SINGLE-USE N=20
PETECHIAE IN VAGINAL WALL	2	0	0
PETECHIAE IN INTROITUS	0	1	1

In baseline exams prior to applicator use, colposcopic findings were observed in 38 (63%) out of 60 exams. The most frequent finding was petechiae (35%), followed by epithelial peeling (27%). After applicator use, 4 colposcopic findings were observed that were considered possibly related to the applicator and were small petechiae in the introitus or vaginal wall *(Table 1)*. There was no disruption of the epithelium observed with any of the study products, and the cases of minor petechiae were not considered clinically significant. Each of the three applicators appeared safe from the perspective of causing severe vaginal or cervical trauma.

Perspectives from the Dominican Republic and South Africa on Re-use and Cost

Five studies have assessed applicator acceptability among developing-country populations. [3,4,5,6,7] While acceptability of both single-use and reusable delivery mechanisms has been documented, little information has been collected on how these preferences might vary in the context of cost, given that single-use, pre-filled applicators are more costly than reusable devices. Issues related to applicator re-use, cleaning, storage, and disposal have also been raised as areas warranting further research.

To better understand these issues in relation to women's preferences for single-use vis-à-vis reusable microbicide delivery mechanisms, PATH conducted studies in the Dominican Republic and South Africa in collaboration with the Institute of Population and Development Studies/IPDS at Profamilia in Santo Domingo and the Reproductive Health Research Unit/RHRU in Durban. The primary objective of these studies was to characterize and prioritize women's preferences regarding applicator features such as cost; single-use and re-use; prefilled and user-filled devices; plastic and paper (cardboard) material; storage; portability; cleaning; and disposal. A secondary objective was to explore how user preferences might differ based on demographic characteristics such as income, marital status, perceived HIV risk, and other socioeconomic variables.

Conjoint analysis was used to estimate the relative benefits or strength of specific product attributes, as well as the overall benefit value (or utility) for different combinations of attributes.[8] Approximately 900 women (449 in the Dominican Republic and 446 in South Africa) were randomly sampled from among clinic

[3] Bentley M, Morrow K, Fullem A, et al. Acceptability of a novel vaginal microbicide during a safety trial among low-risk women. Family Planning Perspectives 32(4):184-188, 2000.

[4] Morrow K, Rosen R, Richter L, et al. The acceptability of an investigational vaginal microbicide, PRO 2000 Gel, among women in a phase I clinical trial. Journal of Women's Health 12(7):665-66, Sept 2003.

[5] Coetzee N, Blanchard K, Ellertson C, et al. Acceptability and feasibility of Micralax® applicators and of methyl cellulose gel placebo for large-scale clinical trials of vaginal microbicides. AIDS 15:1837-42, 2001.

[6] Coggins C, Elias C, Atisook R, et al. Women's preferences regarding the formulation of over-the-counter vaginal spermicides. AIDS 12:1389-31, 1998.

[7] Hardy E, Jimenez A, de Padua K, Zaneveld L. Women's preferences for vaginal antimicrobial contraceptives: III. Choice of a formulation, applicator, and packaging. Contraception 58:245-9, 1998.

[8] Ryan M, Scott D, Reeves C, et al. Eliciting public preferences for health care: a systematic review of techniques. Health Technology Assessment 5(5), 2001.

FIGURE 1. SINGLE-USE APPPLICATOR

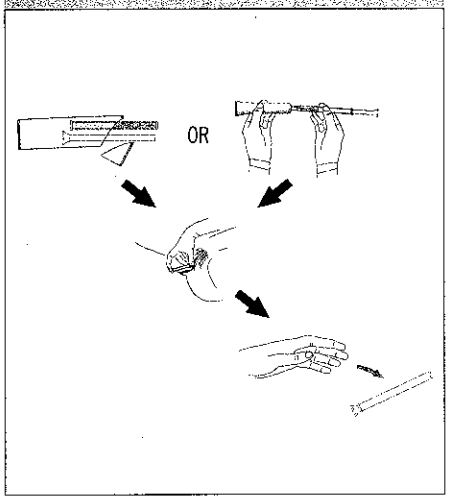
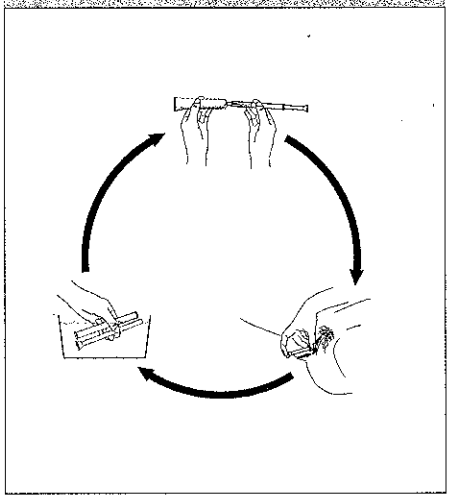


FIGURE 2. REUSABLE APPPLICATOR



Illustrations by Patrick McKern, *Graphic Designer*, PATH

populations and interviewed for this study. No applicator or microbicide products were used by participants; they were instead provided visual and verbal orientations to the varying applicator features *(see Figures 1 and 2)*.

The results from this study indicate that among women in the Dominican Republic, single-use applicators are strongly preferred to reusable applicators, regardless of price. In South Africa, however, while single-use applicators are preferred to reusable applicators when combined with price variables, the single-use/low-price combination is equally valued when compared to the reusable/high-price combination. In this population, there appears to be a direct tradeoff between the perceived safety of single-use applicators and the perceived higher quality of higher-priced products. Comments from women in South Africa concerning safety included: "I prefer a single-use applicator like a condom — to avoid infecting others. Reusable is not really safe." Another respondent noted: "The single-use applicator is safer than the reusable applicator because it won't spread germs. The single use should be cheaper than the reusable." Additionally, while many women in South Africa expressed the opinion that microbicide products should be free or low in cost so that everyone can have access to them, another common remark was that products that are "too cheap" are expected to be of poor quality so that higher-cost products are seen as likely to be more effective.

Table 2 presents the results from two additional questions related to perceived applicator safety. While women in both settings had safety concerns associated with reusable applicators, nearly 50% of the women sampled in the Dominican Republic also had safety concerns about single-use applicators, compared to 4%-5% of women sampled in South Africa. Data analysis for this study is currently

TABLE 2. PERCEIVED SAFETY OF SINGLE-USE AND REUSABLE APPLICATORS

	DOMINICAN REPUBLIC (N=449)	SOUTH AFRICA (N=446)
SOMEWHAT TO VERY CONCERNED ABOUT SPREADING GERMS WITH APPLICATOR		
Single-use	50%	4%
Reusable	89%	94%
SOMEWHAT TO VERY CONCERNED ABOUT EFFECT OF APPLICATOR USE ON OWN VAGINAL HYGIENE		
Single-use	43%	5%
Reusable	90%	89%

DELIVERING MICROBICIDES *(Continued from p. 17)*

under way, and complete results are expected by the end of 2004.

While both single-use and reusable applicators are likely to be needed to address the needs of diverse populations, concerns about the safety of reusable applicators will need to be addressed, since this type of delivery mechanism may well be one of the least expensive options for microbicide delivery.

Applicator Costs

It is highly probable that the cost of microbicide products (microbicide + delivery mechanism) will be a key factor in determining product access in some settings. PATH collected data associated with different delivery mechanisms to assess and compare applicator costs, exclusive of the costs of the microbicide products delivered by each device.

There are limitations to gathering such cost estimates, since they are directly dependent on expected production volume. As volumes increase, (1) manufacturers can reduce their profit margin on each piece, (2) greater investment in manufacturing capabilities can decrease manufacturing costs, and (3) additional manufacturers may be encouraged to become involved if a future market is anticipated.

According to the Rockefeller Foundation's 2002 study, *The Economics of Microbicide Development*, the yearly demand for a first-generation microbicide is projected at approximately 1.7 billion units per year.[9] The prices that are presented below were gathered based on the *current* market for this type of product and may not reflect the cost if the volumes projected in the Rockefeller study are realized. Another consideration is that if a single applicator type or manufacturer were to capture the entirety or majority of this market, the market and manufacturing demands for this product would be significantly altered.

Pre-filled, single-use, plastic applicators are the most expensive microbicide delivery option ($.10-.50 per use), owing to the costs associated with the filling and sealing of these applicators ($.06-.40). User-filled applicators (plastic and cardboard) with a microbicide supply tube are the least expensive delivery option ($.06-.08 per use, assuming 10 uses per applicator and 10 doses per supply tube of microbicide).[10] Cost per use could be reduced further with this application method, depending on (1) the total microbicide volume (number of doses) provided in the supply tube and (2) the number of times women are willing and able to reuse each applicator.

Cervical Barriers and Vaginal Rings as Delivery Systems

Cervical barriers such as diaphragms and cervical caps may also be used for delivery of microbicides, and reusable versions of such devices offer additional options for low-cost microbicide delivery. These products are designed to last for a year or more and range in average price from $15 to $75 in the US market. The vaginal ring, a microbicide-loaded device that is inserted once and designed to provide continuous protection for at least 12 months, may be another important delivery option. Price estimates are not yet available, but this option may be very cost-effective from the standpoint of its potential for continuous 12-month protection with a single application device.

While the first generation of microbicide products is entering Phase 3 clinical trials, several with single-use, pre-filled applicators, additional regulatory guidance is needed with respect to ways alternative applicator designs and delivery mechanisms can provide lower-cost, acceptable options for wide-scale microbicide introduction.

The SILCS Diaphragm

Several new barriers are in development to address some of the historical limitations of existing devices, including the requisite fitting and sizing by a clinician.[11] One such barrier is the SILCS diaphragm, which PATH and its clinical partners have worked to develop over the last 10 years. Employing a user-driven product development process that emphasizes user feedback as the core element of product design, this single-size silicone device is designed to be easier and more convenient

[9] Microbicide Initiative. The economics of microbicide development. New York, NY: Rockefeller Foundation, 2002.

[10] These estimates do not include costs associated with producing the final product (e.g., printing, overwrapping, boxing, microbicide material, and formulation).

[11] Ellertson C, Burns M. Re-examining the role of cervical barrier devices. Outlook 20(2). Feb 2003.

to use than the standard nine-sized Ortho ALL-FLEX® diaphragm. The SILCS diaphragm is contoured to allow for microbicide gel or cream delivery from both sides of the device, providing added protection to both the cervix and vaginal walls. It has completed Phase 1 clinical trials in the United States and is currently being evaluated in acceptability trials in the Dominican Republic, South Africa, and Thailand. Along with existing cervical barrier devices and those under development, it is hoped that the SILCS diaphragm will provide women with an additional delivery option for future microbicide products.

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THE GLOBAL CAMPAIGN FOR MICROBICIDES: A PROFILE

Anna Forbes

The Global Campaign for Microbicides is an international coalition of non-governmental organizations/NGOs working collaboratively to make safe and effective microbicides an accessible reality as soon as possible. Through a broad-based, international effort, we are building support among policy-makers, opinion-leaders, and the general public for increased investment in microbicides and other user-controlled prevention methods. Our tools are advocacy, policy research, and community mobilization.

Our niche in the microbicide world is that we form an interface between the "scientific microbicide community" and the millions of citizens whose lives will be influenced by this enterprise, either as eventual users, trial participants, taxpayers, or individuals at risk of HIV/AIDS. By creating a context that fosters this engagement, we seek to accelerate product development, facilitate widespread access and use, and engage civil society in the scientific process.

We came into being in 1998 as an extension of early efforts by women's health and rights advocates to draw attention to the inadequacy of existing HIV prevention tools and strategies, especially for women. Based in that history, we recognize that a range of prevention tools is needed and that new technologies alone will never be the ultimate solution to the end of the epidemic. Thus we work in parallel to empower communities and change the underlying social realities that condition people's risk.

The formal staffing to support this work is provided by six people based in a Washington, DC, office; one woman based in Brussels; and consultants doing the Campaign's work in India and Africa. The bulk of that work, however, is done in the myriad of large and small NGO offices around the world in which 25 partner organizations and over 200 endorsing groups worldwide are incorporating the Campaign's materials, goals, and strategies into the public education and advocacy work they do every day.

This effort is essential to bringing microbicides — or any other "public health good" such as HIV vaccines, advances in contraception, and malaria and tuberculosis treatments — to market. By highlighting the urgency of the task, educating those in a position to make a difference, and fomenting political pressure for change, these shared advocacy efforts create the political will and momentum needed to propel these less lucrative scientific enterprises forward.

It is the role of advocates to maintain a sense of urgency and ensure that the sober realities of the HIV pandemic are not lost in intricate discussions of regulatory processes and clinical trial design. Advocates monitor the complex deliberations inherent in these stages and create pressure for action if the process fails to proceed expeditiously.

It is also the role of advocates to ensure that views and perspectives of all those who stand to gain or lose from the process have a voice in important decisions. Traditionally, key interest groups —

Attachment 4

New and underused technologies to reduce maternal mortality

*Vivien Davis Tsu**

In July, 2003, maternal health specialists from around the world gathered in Bellagio, Italy, to develop a list of proven and promising technologies, appropriate for low-resource settings, to reduce maternal mortality. We defined technologies as equipment, consumable supplies including medicines, and techniques. While technology, especially in health care, often provokes thoughts of complex, costly interventions, the technologies identified at the Bellagio meeting are mostly simple and inexpensive. What is lacking are resources, human and financial, to scale-up and put proven technologies into widespread use and to assess and document the effectiveness of promising new interventions. There is an urgent need to accelerate the appropriate use of technologies and to reduce the inequitable burden of pregnancy-related mortality borne by women in poor countries.

The 2003 *Lancet* series on child survival highlighted the interventions needed to ensure the health of children worldwide. We would add that saving the life of the mother is one of the best ways to prevent the death of a child. The half million women who die from pregnancy-related and childbirth-related causes every year leave behind at least 1 million motherless children who are all at increased mortality risk.[1,2]

The five major direct causes of maternal deaths worldwide are haemorrhage (25% of maternal deaths), sepsis (15%), abortion complications (13%), eclampsia (12%), and obstructed labour (8%).[3] Many of these causes can be addressed by investing in effective technologies and ensuring their availability to all women in need.

The conference participants selected several underused and promising technologies as being of the most potential benefit in preventing maternal deaths (table). One of the great advantages of many of these technologies is that they are relatively simple, and can be used by health personnel with the skills and training typically found in more remote areas. The table shows the most critical actions needed to advance these interventions. For example, preventive measures and early treatments exist for obstetric haemorrhage, of which there are an estimated 14 million cases every year.[4] If left untreated, post-partum haemorrhage can lead to shock and death within hours. The injection of an oxytocic drug to contract the uterus during the third stage of labour often prevents such blood loss. Ensuring provision of an accurate and sterile dose of oxytocin can be difficult, especially in home and primary health-care settings. A prefilled injection device (Uniject; Becton Dickinson, Franklin Lakes, NJ, USA) overcomes these obstacles by ensuring that health personnel and others with limited training can deliver a sterile, uniform drug dose. Use of this simple technology could save the lives of women at risk of post-partum haemorrhage, even if they live far from a health centre. Initial experience with the device in Indonesia has shown its effectiveness, but assessment in other settings is needed.[5] Additionally, a manufacturer is needed to produce a worldwide supply of oxytocin in Uniject, which is not currently available on a commercial

Priority technologies	Critical next steps
Post-partum haemorrhage:	
Oxytocin in Uniject*	Establish commercial supply; additional operations research
Misoprostol	Operations research; expand availability
Active management of third-stage labour	Operations research; training; incorporation into guidelines
Antishock garment	Clinical research; low-cost production
Intrauterine balloon catheter	Clinical research
Pre-eclampsia and eclampsia:	
Magnesium sulphate	Ensure supply; training; incorporation into guidelines
Vitamins A and E	Clinical research
Calcium	Clinical research (in calcium-deficient populations)
Low-dose aspirin	Clinical research
Proteinuria dipsticks	Operations research on home use; ensure affordable supply
Obstructed labour:	
Simplified caesarean-section techniques	Systematic reviews; training; incorporation into guidelines
Partograph	Training; incorporation into guidelines
Vacuum delivery equipment	Improve equipment design; ensure availability; training for midwives
Symphysiotomy	Systematic review; long-term clinical follow-up
Vaginal cleansing	Additional clinical research
Tocolytics	Clinical research on use during transfer
Misoprostol for induction	Clinical research on safe regimens; develop guidelines
Puerperal sepsis:	
Infection-prevention procedures	Develop and disseminate standards and protocols
Standards for antiseptic use	Update standards for instrument cleaning
Routine vaginal cleansing	Clinical research
Hand-cleansing agents	Ensure affordable supplies and adequate distribution
Vitamin A supplementation	Complete clinical research; operations research on distribution stragegies
Unsafe abortion:	
Medical abortion	Develop and disseminate usage guidelines for mifepristone and misoprostol; ensure affordable supply; cost-effectiveness studies
Manual vacuum aspiration	Make equipment more affordable and easy to sterilise; training; integration into basic primary health care
Pregnancy tests	Make more affordable, feasible for home use
Post-abortion care package	Training; integration into basic primary health care
Emergency transportation and communication:	
Emergency referral systems	Develop and disseminate standards and guidelines; scale-up
Motorised transport	Identify local options; evaluate cost-effectiveness
Clinical protocols and records for referrals	Standardise protocols; introduction into obstetric care
Cellular telephones and two-way radios	Ensure affordable supplies or creative co-financing
Obstetric first aid kits	Operations research to assess designs and effectiveness
Birth preparedness and complication readiness plans	Operations research to assess effectiveness

*For description of Uniject, see text.

Priority interventions and critical next steps

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*For the participants of a conference in Bellagio, Italy, July 8–11, 2003. Conference participants listed at end of report

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scale; we expect the cost would be high initially, but at high production volume the device should cost only US$0·30–0·50 per use.

In the case of eclampsia, a low-technology solution similarly exists to prevent maternal deaths. An inexpensive drug, magnesium sulphate is the most effective means to prevent and treat eclampsia.[6] However, its widespread use, which could prevent many thousands of maternal deaths, needs to be encouraged through the dissemination of updated treatment protocols and through commercialisation and distribution of the medicine itself.

Without the proper tools and technologies, maternal mortality will not decline. We have identified priority technologies and the actions needed to accelerate or expand their availability and use. Full details of the conference will be published early in 2004. Organisations with the financial, political, and human resources necessary to pursue these actions—WHO, World Bank, UNFPA, UNICEF, Partnership for Safe Motherhood and Newborn Health, bilateral and multilateral donors and lenders, private foundations, the private for-profit sector, and non-governmental organisations—should use this list to set priorities and to make progress in reducing maternal deaths. The Bellagio Conference participants have committed themselves to push for immediate efforts to put technology-based solutions to work, and save the lives of mothers worldwide.

Conference participants

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Conflict of interest statement

PATH is the named assignee on patents covering the Uniject device, but receives no royalties from sales of the device. V Tsu, an employee of PATH, has no personal financial interest in any of the technologies mentioned. G J Hofmeyr has discussed modifications to the vacuum extractor apparatus with PATH staff; he has no financial interest at present.

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Forced migrants—turning rights into reproductive health

Linda A Bartlett, Susan Purdin, Therese McGinn

Worldwide, more than 35 million people live as forced migrants. These are people displaced from their homes by complex humanitarian emergencies—crises that result from environmental hazards or armed conflict combined with adverse social, economic, and political influences.[1] Forced migrants may find refuge within the boundaries of their own country (internally displaced persons) or across an international border (refugees). Some of these refugees are granted asylum to resettle in other countries. In this paper, we focus on the right of access to reproductive health care for forced migrants and, in particular, for the majority who live in conflict zones in the developing world. We discuss the extraordinary risks to reproductive health faced by forced migrants, and the obligation of humanitarian agencies to respond to reproductive and sexual health needs.

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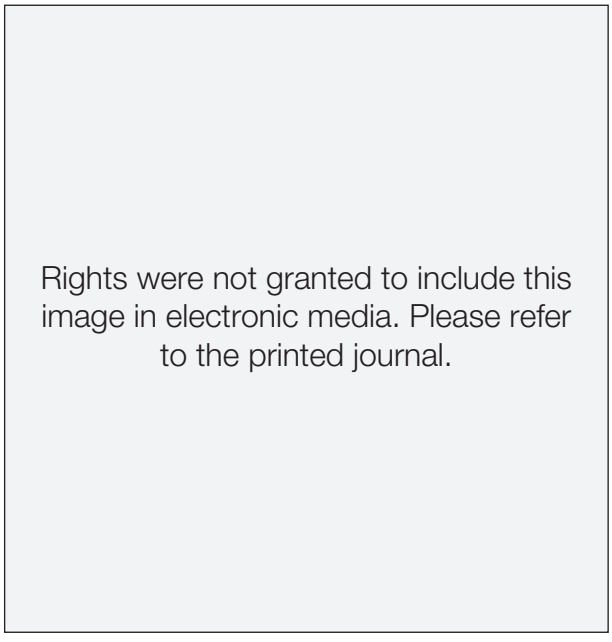

Still Pictures

Afghan refugees in a camp in Pakistan
Women's status can complicate provision of reproductive health care to migrants.

Attachment 5

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Achieving appropriate design and widespread use of health care technologies in the developing world. Overcoming obstacles that impede the adaptation and diffusion of priority technologies for primary health care

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Abstract

Objectives: To identify and describe constraints facing the development and dissemination of technologies appropriate for public health care challenges and solutions in the developing world. *Methods:* Review of lessons learned in development and introduction of numerous health technologies as experienced by a non-profit organization working on technologies for 25 years. *Results:* Many obstacles prevent appropriate technologies from reaching widespread use and acceptance. These include low profit margins in developing world markets, regulatory constraints, and the need for systems changes. Strong public/private-sector partnerships and realistic approaches to working in these environments make a difference. *Conclusions:* There is a growing awareness of the need for new technologies and experience with strategies that can make them happen. Some technologies with documented value for maternal care in developing world settings appear to be stuck short of widespread acceptance and use. Understanding the factors impeding their progress can enable the public sector and its collaborators to organize and facilitate their progress more effectively.

Keywords: Technologies; Developing countries; Appropriate design; Private-sector partners; Introduction; Mainstreaming

1. Introduction

1.1. What are 'health technologies for the developing world'?

Technology can be defined in a variety of ways. In this paper, 'technology' refers to products that are bought and sold (not procedures). The paper discusses the means by which suitable technologies are developed, made, distributed, and adopted, and become standard in the delivery of health care to resource-poor developing world populations. Almost all such technologies get stuck somewhere in this pipeline. The objective of the paper is to identify common blockages and suggest ways for overcoming them.

1.2. Failure of markets

The private commercial sector is adept at generating suitable and affordable technologies and getting them to the people who need them. Users of these technologies, however, must be able and

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willing to pay a price that provides a reasonable rate of return on the investment needed to create, make, and market the products. Public health institutions and the populations they serve in low-income countries have many needs, but they lack resources and therefore do not offer attractive markets for investment. Without money, need does not translate into demand.

It follows that the simplest approach to making suitable technologies available would be for the public sector to define the need and guarantee the market. With such guarantees, all needs could and would be met by the commercial sector. The public sector rarely takes such risks, however; a global crisis that threatens the health, peace, or prosperity of the wealthy industrial nations is often required to prompt action.

To overcome market failures in the absence of market guarantees, the public and donor community must partner with commercial entities to share the costs and risks of designing, validating, marketing, and distributing suitable technologies.

The following section describes the product pipeline, and pays special attention to the major blockage points where even well-targeted technologies can languish.

2. Achieving appropriate design

2.1. Essential role of the public sector

In developing world health care—particularly in primary health care—the technologies used in the industrial world are often inappropriate [1]. They usually require well-functioning infrastructure—power, clean water, support systems, waste collection—as well as high levels of training and supervision, and high patient mobility and compliance. These conditions of use are often unavailable in low-income countries. Additionally, the health care priorities and spectrum of diseases in low-income countries differs from those in industrial countries, and requires unique diagnostic, treatment, and prevention tools.

Some needs can be met by adapting existing technologies. Others require new design. In either case, the health products industry has little incentive to send its market researchers into the periphery of developing country health programs to assess needs and define products. The public sector must do it. This is the first sticking point.

Needs assessment and performance criteria. Universities, non-governmental organizations (NGOs), and development agencies are profound sources of knowledge about health needs in low-income countries. Some researchers go beyond an exploration of need to define a solution—an intervention that may include a technology. The performance characteristics of this technology may not be adequately elucidated, however, and the approach may suffer from a lack of international consensus.

Arguably, defining the performance characteristics for a needed technology is the most important task for the non-commercial sector. The ideal output is a clear description of minimum performance that a technology will require to solve a problem (for example, effectiveness, conditions of use, cost, and durability) [2]. That description should be validated in diverse settings and broadly endorsed by the international public health community. This information can prompt donors to support product development and enable developers in the commercial and non-profit sectors to move forward with design.

Achieving consensus on solutions can be a complex and expensive exercise requiring many international meetings, publications, prioritization exercises, and endorsements by key agencies. Resistance to change and fear of innovation are often evident during this process. In addition, the ultimate users of the product may have very different priorities for a device than providers or purchasers of the product do. In some cases, consensus on solutions can only be achieved or enabled by the pilot introduction of prototypes. Such prototypes are only feasible for technologies that can be produced on a limited scale without high capital investment.

Consensus is achieved more easily if the need is within the scope of a high-profile global or regional program (such as immunization, AIDS, tuberculosis, or family planning). Outside these concentrations of resources and central coordination, building consensus can be more difficult. One long-term strategy for safe motherhood and other

such orphan areas of health care that have not received such high levels of attention is to raise them to a higher level of priority in the global community.

Economic sustainability—an essential criterion. Appropriate design is essential to but not sufficient for the success of a technology. The technology must also be available for the long term, affordable, and of adequate and consistent quality. Except in rare circumstances, this requires that the technology be undertaken by the commercial sector at some point. The most critical factor in achieving transfer to a commercial partner is reasonable assurance of a market (see below). At the design stage, there are also some important considerations, collectively known as design control, that include excellent record keeping, attention to manufacturability, raw material availability, and intellectual property. The progress of a technology is often impeded by these issues.

2.2. Design control

Wherever original design takes place, it must be as rigorous as in the commercial health industry setting. Almost all health products require some level of regulatory clearance or pre-qualification. Recent design control regulations, the increasingly stringent standards of internal review boards (human subjects ethical review), and future licensees or collaborating manufacturers demand a prescribed and disciplined approach to record-keeping and process. Consequently, it is more difficult for a lone developer to advance in the process of design and development. However, there are possibilities for early collaboration, particularly by technology-oriented NGOs, collaborating commercial companies, or contracted service groups. Also, some health care service providers are willing to test concepts, join focus groups, and conduct design-stage clinical trials.

2.3. User as co-designer

The only sure way to fully meet user needs is to involve the user in the design process. Design concepts must be challenged in a variety of settings, cultures, and programs. Cycles of testing and refinement are often needed, particularly for technologies involving critical human factors (e.g. devices and diagnostics). Drugs and vaccines may also perform differently in various cultures or with different levels of nutrition, co-infection, or external conditions. The participation of target populations in these trials is indispensable.

2.4. Donor as venture capitalist

In the past, donors generally have not been keen on underwriting design and development of new health technologies. Their interest has increased in recent years, but the levels of funding are still not sufficient by commercial standards, which leads to long development periods, premature expectations, and donor fatigue. Donor interest may be stimulated by demonstrating:

- A clear and well-supported understanding of the need.
- Well-developed technology performance characteristics to meet the need.
- A network of qualified partners willing to commit if resources are made available.
- A realistic view of the hurdles involved.
- A credible projection of the value in terms of benefit that could be attributed to the technology once in widespread use.

The significant investment in new technologies made by some donor or development agencies is often not recognized or supported by other agencies, or even by implementing divisions of the same agency. Bridging these institutional policy gaps between innovation and implementation can help overcome impediments to the diffusion of new technologies for developing world health programs.

2.5. Public–private partnerships for design

Early involvement of a competent and committed private commercial firm can help overcome the impediments noted above [3]. Industrial world health firms of all sizes may become involved in advancing products for developing world health if:

1. The need is clearly defined.

2. A reasonable consensus exists among the international public health community.
3. A meaningful collaboration is offered to raise funding, design, field test, align policies, and promote the product.

Many local health product firms in emerging countries (e.g. India, China, Indonesia, and Brazil) have met international quality standards in production and are willing to add new products for local and international markets, although their research and development capacity may be limited.

A private partner at the design stage may not be the right partner for later stages of the product pipeline (such as marketing), however. Therefore, all parties should recognize the need for multiple partners and envision various scenarios of collaboration to clarify the roles of each partner.

Adapting existing products. A firm may be more willing to enter partnerships for developing world applications if they already have an adaptable product or platform. Start-up companies are less disposed than established companies to such collaboration because their survival depends upon achieving early returns on investment; they are focused on more immediate and lucrative markets. However, start-ups often possess innovative technologies that could solve intractable problems in developing world health. While it is possible to induce these innovators to collaborate, the public sector investment is higher. These small firms are at risk when access to financial resources is limited [4], suggesting the need for donor-supported venture capital and financing programs.

3. Progressing from design to product

3.1. Managing intellectual property (IP)

Independent assessment and management of intellectual property is absolutely critical in public-private partnerships for technology. Commercial companies must ascertain their 'freedom to practice' according to issued and pending patents in industrial and target low income countries. Donor investments can be lost if commercial collaborators lose their property rights to other claimants through litigation.

Also, firms sometimes change ownership, leadership, and business plans; today's great collaborator can be tomorrow's most problematic partner. Carefully worded agreements therefore must be executed up front in all these partnerships. These agreements must ensure public health access to the technology, independent of what happens to the commercial partner. They also address critical issues such as affordability, diligence, and quality, as well as spelling out the roles of the partners. For some firms, just negotiating the agreement can be a deterrent to collaboration, since the firm may not have experience with international donor requirements or legal language.

The parties representing the needs of low-income countries are in a stronger position if they can offer intellectual property to the commercial partner, even more so if the inventions also have value for industrial country markets. In this case, the parties can negotiate strong terms in favor of the developing world markets and persuade the firm to absorb more development costs in exchange for rights to industrial country markets. Technologies in the public domain offer no protection to commercial firms and are consequently harder to 'sell' to potential commercial partners.

However, technologies that are exclusively controlled by one commercial party can create a monopoly on supply. International and bulk procurement agencies dislike monopolies because there are no competitive forces to control price and because United Nations agencies (in particular) shy away from endorsing a single brand. This creates a paradox because single parties will often control inventions of value to developing world health. Furthermore, inventions developed by the non-profit or public sector may have to be offered exclusively to a commercial partner if the amount of capital required to scale up, manufacture, and market is very high and/or the scale of demand does not justify multiple producers.

To reduce the risk of escalating prices from a monopoly, the parties can devise a plan to stimulate competition in the longer term. This is a risky strategy and must be implemented with care; it may discourage innovation directed at developing world health care needs or render a product economically unsustainable. If the market is stimulat-

ed by the innovation, other suppliers will sometimes come forward with alternative designs without any prompting.

3.2. The role of 'bridging' organizations

A few organizations manage public/private partnerships to advance technologies on behalf of the public health sector. As donor investments in technology increase, and design control, licensing, IP, and access issues grow more complex, more such organizations will appear. These organizations function similarly to commercial product development organizations, except that they are supported by donors and seek to achieve social rather than financial returns on investment. Bridging organizations are more flexible and can manage uncertainties, change direction, make trade-offs, and respond to opportunities more effectively than bureaucracies. They will not always be successful but they can significantly reduce the risks associated with making appropriate technologies available to low income countries.

3.3. Validation and revalidation: building the evidence base

There is no certainty in predicting when a technology designed for developing world use will be perceived as sufficiently validated to warrant general acceptance. However, the process can be made more efficient by careful staging of field trials and selection of collaborators, well-designed operations research (e.g. for cost-effectiveness or local approval), targeted publication and communication of results, and early initiation of policy dialogue with key gatekeepers. Model programs can sometimes be effective at gaining widespread attention and, in the best cases, can scale up to national adoption. Technologies with benefits that are easier to demonstrate and observe will generally spread faster. Ultimately, innovative technologies require a critical mass of champions to overcome the endemic resistance to change in public health programs.

Creating and supporting product champions. Owners make great promoters. If influential people believe in the benefits of a technology and feel that they have a stake in its success, they will use their networks to spread the word. Fostering champions requires good evidence, good management, transparency of process, and willingness to share the ownership of the project. In practice, this unlimited level of openness has to be balanced against the confidentiality that is often necessary for commercial collaboration and intellectual property management. However, closely 'branded' technologies will generally have a harder time achieving widespread acceptance in the international public health community.

3.4. Regulatory barriers

The Global Harmonization Task Force, founded by Japan, the European Union, United States, Canada, and Australia, has developed a 'gold standard' for health products all over the world. Many National Regulatory Authorities (NRAs) also depend on these standards. Donors investing in technologies for developing world health programs can be concerned that bypassing these authorities may lead to concern about double standards. Yet there are advantages and disadvantages to the strict requirements of these major regulatory bodies.

When is industrial world licensing appropriate? While regulations offer unmatchable assurance of safety and quality of design, development costs and time can double or triple if technologies are subjected to the process required for licensure by industrial world bodies. Technologies with relatively low development costs (like immuno-diagnostics) may become unaffordable as a result. Additionally, products with very little application in industrial countries may gain little value from this level of regulatory clearance, particularly if they are to be manufactured in low income countries (where the NRAs will control manufacturing quality). Some products of enormous value to low income countries have been taken off the market because of a level of risk that is unacceptable to the industrial world, even though the benefit-to-risk ratio was quite different and overwhelmingly life-saving in low income countries (e.g. rotavirus vaccine).

The complexity of the technology and the extent of innovation involved often define the regulatory strategy. The regulatory strategy for a developing world technology must be considered on a case-by-case basis to achieve the optimum balance among safety, affordability, availability, and accessibility.

Altering standards of practice. The new technology or intervention often requires a change in the standard of practice at the broadest level of developing world health care service delivery systems. The costs and level of effort associated with changing behavior in every primary and first referral level facility is formidable—arguably much higher than the cost of developing a new technology. This burden can be eased considerably if: (1) The technology requires no change in practice (e.g. the substitution of one vaccine by a better one). (2) The technology controls behavior (e.g. auto-disable syringes). (3) The technology requires only a minor adaptive change that is compatible with or simplifies current practice (e.g. oxytocin in the Uniject™ device). (4) The technology is to be used frequently so that new skills are quickly reinforced (in contrast to emergency technologies that may be used only rarely in peripheral practice).

4. Finding a manufacturing partner

As mentioned previously, the global health community must work with commercial companies to ensure sustainable supply of high-quality products. Sooner or later, the appropriate technology must be converted to a manufacturable product, scaled up, produced efficiently, and distributed to the programs and people in need. The engines of private enterprise—profit and an expeditious return on investment that equals or exceeds that of another product or market—drive these commercial organizations. Persuading a competent firm to take on a product aimed exclusively at developing world health programs is a challenge. These companies are generally most concerned about the market: whether it exists, how big it is, and who actually selects and buys the products.

4.1. Measuring the market

The people who use, the people who choose, and the people who pay the dues. In the international and developing world public health sector, entities selecting suitable technologies (through endorsement, recommendations, and guidelines) are often separate from those that actually buy the products. Still other people use the products. The communication among these three entities is generally limited. Each might view the value of the product quite differently: one in terms of global public health impact, another in terms of procurement costs, and another in terms of local acceptability and advantage over alternative interventions. Often, the whole-systems cost-effectiveness equation does not come into full perspective during these transactions. Instead, several factors play a dominant role in the acquisition of technologies: direct donations of technology or aid tied to products from the donor country (which buys the product), the manner in which the product life-cycle costs are distributed across sectors or levels of the health care system, and the influence that sales representatives can have on the process. Procurement decisions based upon comparative technology assessment are not common at the local level. All of these factors complicate the process of assessing markets and greatly extend the ramp-up from early adopters to wide-scale use. Nevertheless, some measure of the market is needed to convince manufacturing partners to get involved.

Demand versus need. The developing world's need for almost all technologies is extremely high, but the funds and ability to absorb the technologies are severely limited. Manufacturers are primarily interested in demand—that is, consumers' willingness and ability to buy. Latent demand is only important if it can be converted to real demand at reasonable cost. Technology assessment and procurement groups are generally the parties that assess demand, but unless the technologies benefit an internationally coordinated program or campaign, the selection and procurement decisions are usually made at the national or even sub-national level. These local markets can be extremely diffuse and costly to reach, influence, and aggregate into an economically sustainable enterprise. Unless the

public sector is willing to take on the marketing and distribution of the product, the complexity and uncertainties associated with these tasks relative to the value of the market are formidable obstacles to many international firms.

Local manufacturers and distributors may be better positioned to market technologies that depend on local networks and influence for successful introduction and uptake [5].

Central and local procurement. Health care products are purchased by international agencies [e.g. the United Nations Population Fund (UNFPA) and United Nations Children's Fund (UNICEF) Supply Division], bilateral agencies [e.g. the United States Agency for International Development (USAID)], and a variety of international organizations and programs specializing in a particular health care area such as immunization, blood banking, family planning, tuberculosis, and malaria. These entities rely on technology assessments carried out by the World Health Organization (WHO) and/or their own technical divisions. The international procurement agencies generally respond to requests from client countries for specific technologies, although those products generally must be approved by WHO and by the procurement agency. (Although these agencies may endorse a certain generic category of technologies and may decline to supply others, they do not actively promote the use of specific products.) Many well-validated technologies get stuck because they lack substantial assessment data or advisory or promotional messages coming from these agencies or from other sources. Consequently, awareness of and confidence in the technology at the country level remain low and no stream of requests is forthcoming.

The power of special global programs. New technologies usually diffuse much faster in vertical, centrally coordinated programs. International consortia can mobilize funding and coordinated action around a particular disease or strategy. National authorities then agree at the beginning to design and build their programs according to a set of standardized protocols and products selected through a consensus process of technology assessment, training, communications, and central procurement. The manufacturers' tasks of submitting products for assessment and estimating demand are made easier by this 'one-stop' marketing arrangement, although the extent to which the product meets the need and is cost-effective relative to alternative interventions becomes very critical because of its potential global impact. Also, technologies can become 'locked in' to these programs, which limits innovation, particularly if the new technology requires a change in standard practice at the service delivery level.

Commercial appeal. A technology may have special appeal for a manufacturer if:

- It has an application in wealthy countries as well as low-income countries.
- It fits in well with their current product line.
- It offers access to new markets for its other product lines.
- The market is potentially very large, notwithstanding the uncertainties.
- It serves a pressing public relations need.

4.2. Due diligence in partner selection

Some carefully designed and validated technologies have been sidelined because they have been placed in the hands of a manufacturing partner who is unable to achieve availability, quality, or affordability. Manufacturing businesses change ownership or leadership with surprising frequency. Some fail altogether, some do not perform to the terms of their agreement, and some experience insurmountable obstacles. To manage these risks, the group representing public sector interests must perform due diligence when selecting partners, carefully developing agreement terms that provide for the above contingencies, establishing agreed-upon milestones, and performing audits. Most importantly, the public sector partner must ensure close communication and collaboration during the introduction and mainstreaming of the product.

4.3. Sharing the risk

The manufacturing partner will expect the public health sector or its representative organizations to take a share in the investment and risks of the project. Negotiations with prospective manufacturing partners will ultimately depend on the designs,

data, resources, and commitment that the public health representative brings to the table. Although the manufacturer may recognize a public relations value of a public/private partnership, they cannot tolerate a losing proposition or an impossible mission.

5. Introducing technologies

Introduction should begin quite early in the design and development process. Collaborators involved in the design or validation stage can identify with the technology and its potential impact, become early adopters, and act as powerful advocates for widespread use. Data gathered for design control, validation, and licensing purposes can build the evidence base and help persuade donors, gatekeepers, and decision-makers of the value proposition.

5.1. Developing the value proposition

Why should health care program managers and international agencies subscribe to the new technology? Why is the technology better than existing or alternative interventions? What major problems does it solve? Because change is expensive and complicated to implement at the periphery of the developing world health care system, the impact of the innovation must be substantial and the costs must be absorbable. This value proposition must be clear and well communicated for the technology to be successfully adopted.

Benefit. Some benefits are obvious; others are less apparent. The public health community may not recognize benefits that seem obvious from the technology developer's point of view. Many extensive, systemic, and soluble problems that are commonly observed and anecdotally reported may require considerable time and effort to become officially recognized. Furthermore, the data-collection effort required to put the problem on the public health agenda may be beyond the scope of the technology developer or champion. Unsafe injection serves as one example: Visitors to health care facilities observed the risks of unsafe injection for a decade until the volume of concern finally prompted a broad analysis of the problem and gave credibility to the safety syringe (e.g. auto-disable) technologies that offer quick and effective solutions.

Some technologies offer system benefits, which are less tangible and harder to measure. For example, the benefit of pre-filled, single-dose injection systems (like the Uniject™ device) for delivering uterotonics or vaccines includes simplicity of use, which allows less trained village health workers to administer the medicament safely and effectively in low-infrastructure settings. Program managers may not concede that the complexity of current regimens is a problem, and they may not be willing to pay the extra cost of changing from multi-dose to single-dose formats, or changing from standard to non-reusable injection devices. Overcoming this resistance may require local trials, model programs, and documented results from routine use in other countries.

Low frequency of use and consequent low repetition of practice can erode the value of some technologies. This may be particularly true of life-saving technologies used in obstetric or neonatal emergencies. At the level of the village midwife, the needs for these technologies may be so rare that training is not reinforced by practice. As a result, the technology falls into disuse as service providers forget the training and lose confidence in their ability to manage the technology. Reinforcing exercises or training must be planned to raise the confidence of program and financial managers.

Clearly, it is the perceived—rather than real—benefits that matter for technology introduction. The value proposition for a technology needs to be continually updated as new data become available, so that perceived and real benefits merge as early as possible in the introduction process.

5.2. Economic analysis

The potential benefits may be convincing, but the costs also must be ascertained.

Whole system costs. The life-cycle cost of a technology may not be obvious to a decision-maker. Depending on the technology, the cost may include procurement, delivery, training, fuel, maintenance, repair, depreciation or replacement, and

disposal. Introduction of the new technology or intervention generally requires a ripple of other changes including supporting technologies (e.g. regulated-dose injection technologies to support the introduction of magnesium sulfate) and services, as well as changes in protocols and procedures, budget allocations, and personnel. An analysis of these changes and associated costs in a variety of typical settings is essential to an understanding of value.

If the introduction of a technology can reduce the whole-system costs, or if it can save significantly more lives or gain disability-adjusted life years (DALYs) at the same or modestly greater system costs, the technology is justified. However, these results may not be persuasive to purchasers, program managers, or service-facility supervisors, if their share of the overall costs increases as a result.

Sector costs. Efforts to introduce point-of-care diagnostics for infectious disease offer a lesson in the importance of determining which groups pay for what. Point-of-care tests can have great benefits because the results are available while the patient is still in the health center, allowing providers to offer immediate treatment and conserve drugs. Although primary health care service providers appreciate the diagnostics, many countries allocate budgets for clinical testing only to laboratories. As a result, health centers must decide whether to buy rapid tests out of their own budgets or continue to send samples to the laboratory and forgo the advantage of point-of-care testing. They often choose the latter. The laboratory has an incentive not to endorse or encourage the use of point-of-care tests. All these vested interests influence national health budget allocations.

Clearly, introducing some technologies requires substantial system reform. International agencies are best positioned to provide the necessary influence. Early endorsement of the technology by—and strategic collaboration with—relevant WHO divisions becomes particularly important with discontinuous ('paradigm-shifting') innovations. The capability and resources of different WHO divisions vary greatly, so technologies that fit into coordinated central programs with a global emphasis are more likely to benefit than those for health care problems that are not on the 'center stage.'

5.3. Working with early adopters

Early adopters of a technology—e.g. groups or programs that were previously involved in design-stage trials or validation of the technology—are invaluable and deserve attention. As collaborators, early adopters can help refine and operationalize the technology, develop training protocols and materials, generate cost-benefit and impact data, and act as advocates and showcases for the value proposition.

Model programs. Large demonstration projects with district, state, or even national scope can be built around the good offices of pioneer and early adopters. These model programs can test and demonstrate the scalability of the technology and the associated system changes. Successful model programs can be compelling in shifting policy, adjusting budgets, and bringing about a widespread change in standard practice.

Spreading the word. Advocates must disseminate information about a new technology's usefulness and impact. Decision-makers at all levels must be aware of the technology and its value proposition. Mainstream adopters must hear about it from multiple and credible sources. They must have opportunities to observe it in action without taking risks. They must become aware that it is a 'best practice.' This type of 'critical mass' of communication about a technology's demonstrated benefits is essential to moving beyond the early-adoption stage.

5.4. Working with the gatekeepers

A few international organizations play an essential, normative role in developing world health care practices. They establish best practices and develop guidelines for interventions, training, essential drugs, equipment, and supplies. Sometimes they carry out technology assessments and make recommendations for specific technologies. In a few cases (e.g. vaccines), these organizations audit and qualify manufacturers. WHO is the most notable of these groups and has the broadest scope,

as it spans all health topics (although not with equal intensity). WHO review and endorsement of revised guidelines for a new technology are essential to ensuring broad applicability, raising confidence of national program managers, and enabling central procurement agencies like the UNICEF Supply Division to purchase and distribute the products.

In the last decade, WHO has become more adept at advancing technologies, although they are still constrained by policy when dealing with individual commercial entities and products. They are also spread very thin, so that one staff member may cover a wide range of specific health problems. Finding and establishing working relationships with relevant divisions and key staff members early in the design and development process is very valuable and encourages a continuing dialogue. As a result, the technology and its potential impact can be discussed at international workshops and consultations, leading to a wide scrutiny and understanding of the value proposition among the relevant experts in the international consulting and advisory community.

These interactions are critical in validating the technology; raising donor interest; identifying testing sites, collaborators, and early adopters; and ultimately justifying the technology and changing standard practice and guidelines to accommodate it.

6. Mainstreaming

"In health care, invention is hard but dissemination is even harder" [6].

Dissemination of innovation occurs quite reliably according to the S-curve model. The technologies are initially taken up by innovators, who consist of a very small portion (approx. 3%) of the population who are attracted to new technologies and are willing to take risks, but are not usually influential. The innovators are observed by another segment (approx. 12% of the population) termed 'early adopters.' Early adopters are often opinion leaders who are willing to try out new ideas and who can convince others to adopt them. They influence the 'early majority' (approx. 35%), which is more cautious and relies more on personal networks than scientific data to assess the risks in taking on a new technology. The 'late majority' (35%) will only take up an innovation when it appears to have become standard practice and has been taken up by local early-majority practitioners. The remainder of the population (15%) is likely to resist unless forced to change by regulation.

With regard to health care programs for low-income countries, this model is complicated by the decision-making processes of the gatekeepers who influence the choice of technology, the donors and purchasers who buy the technology, and the users. Each group has its own early- and later-stage adopters who have to be dealt with in the context of their own institutional and policy environments. The actions or inaction of these three stakeholder groups can profoundly affect the process of mainstreaming technologies for developing world health care, so each must be taken into account in the planning and process.

For mainstreaming, we are concerned with moving the technologies from early adopters to early- and late-majority users.

6.1. Creating demand and reducing uncertainty at the national and program levels

Establishing policy and guidelines at the level of WHO or other normative organizations is essential but will not guarantee that the technology will be taken up across the developing world.

Field demonstrations. National decision-makers often need convincing through observation and practice that is closer to home. Programs should make every effort to facilitate local trials and exchanges of experience between national health care program leaders. Training materials and job aids, free products for trial, trial protocols, and technical assistance can all be useful in promoting local testing.

Programs must tolerate—and, in many cases, encourage—local adaptation of the materials, protocols, or support systems (and sometimes the technologies themselves) within limits that do not jeopardize safety and effectiveness. Local adaptation encourages ownership of the new intervention and is more likely to lead to adoption.

Policy dialogue. Local policies, practices, budgets, and guidelines need to be adjusted to the new technology. Often, these changes can be facilitated through central guidelines and consultations supported by local champions.

Need for adequate and consistent supply. The mainstreaming process can be severely disrupted if the supply of the technology cannot meet the early demand. Since market forces are often contorted in developing world public health markets, it is not always possible to keep up with demand. An entity acting on behalf of the public sector interests must pay attention to the supply and demand so that interventions to redress the balance can be made in a timely way.

7. Conclusion

Many hurdles impede the development, introduction, and dissemination of technologies that are appropriate for developing world public health care programs. The international public sector, however, is not yet fully prepared to support or facilitate these processes. Nevertheless, there is a growing awareness of the need for such technologies and a growing experience with the strategies that can make them happen.

Some of the technologies with documented value for maternal care in developing world settings appear to be stuck short of widespread acceptance and use. This paper may give some understanding of the factors that may be impeding their progress as we discuss ways to move them forward.

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